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AUTHOR – AUTEUR

Full Name of Author – Nom complet de l'auteur: OSSAMA METWALLY EL-BADRY

Date of Birth – Date de naissance: 12/12/1954

Canadian Citizen – Citoyen canadien: ☐ Yes / Oui ☒ No / Non

Country of Birth – Lieu de naissance: Egypt

Permanent Address – Résidence fixe: Faculty of Pharmacy, Cairo University
Egypt

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PYRIDINE AND REDUCED PYRIDINE ANALOGS AS HISTAMINE H_2-RECEPTOR ANTAGONISTS

by

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A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
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(Signed) Ossama Metwally El-Badry

PERMANENT ADDRESS: Organic Chemistry
Department
Faculty of Pharmacy
The University of
Cairo-Kasr El-Eini
Street, Cairo-Egypt

Dated July 25, 1985

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled "PYRIDINE AND REDUCED PYRIDINE ANALOGS AS HISTAMINE H_2-RECEPTOR ANTAGONISTS", submitted by OSSAMA METWALLY EL-BADRY, in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Sciences (Medicinal Chemistry).

E. E. Knaus
(Supervisor)

D. L. J. Clive

Frank S. Abbott

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ABSTRACT

A class of heterocyclic compounds of general structure Het-$CH_2SCH_2CH_2Y$, which possess potential bioisosteric Het and Y groups, have been designed for use as histamine H_2-receptor antagonists. Compounds having pyridinyl, 1,2-dihydropyridinyl (108-125, 157, 158, 162, 168, 177, 178) and 1-methyl-1,2,3,6-tetrahydropyridinyl (127) Het moieties in conjunction with urea (103, 159), thiourea (104, 160, 169-172), cyanoguanidine (105, 161, 173-176), nitroethene (142-156) and carbomethoxyguanidine (167) Y groups were synthesized and evaluated as histamine H_2-receptor antagonists to develop structure-activity correlations.

The N-methyl-N'-[2-(pyridinylmethylthio)ethyl]ureas 103, thioureas 104 and cyanoguanidines 105 were prepared by reaction of (2-aminoethylthiomethyl)pyridines 102 with methylisocyanate, methylisothiocyanate and S-methyl-N-cyano-N'-methylcarbamimidothioate respectively. The reaction of 102 with bis-thiomethylnitroethene and then a cycloalkylamine, phenylisocyanate, phenyl (cycloalkyl, n-alkyl)isothiocyanates and N,N'-dimethoxycarbonyl-S-methylisothiourea afforded N-[2-(pyridinylmethylthio)ethyl]-N'-(cycloalkylamino)-2-nitro-1,1-ethenediamines 142-156, N-phenyl-N'-[2-(pyridinylmethylthio)ethyl]ureas 159, N-phenyl (cycloalkyl,n-alkyl)-N'-[2-(pyridinylmethylthio)ethyl]thioureas 160, 169-172 and N,N"-dimethoxycarbonyl-N'-[2-(pyridinylmethylthio)ethyl]-guanidines 161 respectively. Alternatively, reaction of thioureas 160 and 169-172 with lead cyanamide also afforded cyanoguanidines 161 and 173-176 respectively. The 1,2-dihydropyridinyl analogs 108-125, 157

158, 162, 168 and 177-178 were prepared via reaction of the corresponding pyridinyl derivative with methyl chloroformate, phenyl chloroformate or di-tert-butylcarbonate with sodium borohydride in methanol at -65°C. The sodium borohydride reduction of the N-methylpyridinium salts 126 at 0°C in ethanol afforded the N-methyl-1,2,3,6-tetrahydropyridinyl derivatives 127.

The stereochemistry of N-[2-(pyridinylmethylthio)ethyl]-N'-(cycloalkylamino)-2-nitro-1,1-ethenediamines 138 was investigated to determine the stereochemistry of the substituents attached to the olefinic bond. A Nuclear Overhauser Enhancement (NOE) difference ^1H nmr experiment suggested that the terminal cycloalkylamino substituent was *cis* to the proton and *trans* to the nitro substituent on the ethene group.

These structural modifications to the lead compound 9 were investigated to determine 1) The effect which replacement of the imidazole ring of cimetidine (9b) by other heterocyclic ring systems such as pyridinyl, 1-methoxycarbonyl(phenoxycarbonyl, t-butoxycarbonyl)-1,2-dihydropyridinyl and 1-methyl-1,2,3,6-tetrahydropyridinyl had upon H_2-antagonist activity, 2) The relative activities within an isomeric series of pyridinyl, 1,2-dihydropyridinyl and 1-methyl-1,2,3,6-tetrahydropyridinyl analogs, 3) The importance of charge distribution in the pyridinyl, 1,2-dihydropyridinyl and 1,2,3,6-tetrahydropyridinyl ring to interaction with the histamine H_2-receptor, 4) The effect of replacing the terminal methyl substituent in the side chain of cimetidine (9b) or ranitidine (9e) by a phenyl, methoxycarbonyl and other alkyl or cycloalkyl substituents and replacing the terminal methylamino moiety by cycloalkylamino rings as pyrrolidino, 1,2,3,6-tetrahydropyridinyl, morpholino, piperidino and hexahydroazepinyl and 5) The bioisosteric relationship between urea, thiourea, cyanoguanidine and nitroethene moieties as well as the pyridinyl and 1,2-dihydropyridinyl ring systems.

The histamine H_2-receptor antagonist activity of selected compounds was determined using the chronotropic response of the guinea-pig right atrium. The H_2-receptor antagonist activity was quantitated from the dose-dependent displacement of the histamine concentration-effect curve. The pharmacological test results obtained indicated that the relative activities within an isomeric series of thiourea 104 and cyanoguanidine 105 analogs was 2-pyridinyl > 4-pyridinyl > 3-pyridinyl. Elaboration of the pyridinyl ring to a 1-alkyl(aryl)oxycarbonyl-1, 2-dihydropyridinyl ring reduced activity whereas conversion to a 1-methyl-1,2,3,6-tetrahydropyridinyl ring 127 abolished activity. Compounds having a 2-nitro-1,1-ethenediamine Y moiety displayed H_2-antagonist activity whereas those having a N,N"-dimethoxycarbonylguanido Y group 161 were inactive. The test results suggest that affinity for the H_2-receptor is due, at least in part, to cooperative and dependent interactions of the molecular substructures, which include the Het and Y moieties. The structure-activity correlations for H_2-antagonist activity have been discussed in detail.

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LIST OF ABBREVIATIONS

bp	boiling point
cm	centimeter
°C	degrees Celsius
$CDCl_3$	deuterochloroform
DMSO-d_6	hexadeuterodimethyl sulfoxide
g	gram
h	hour
^1H nmr	proton magnetic resonance
ms	mass spectrum
mp	melting point
mg	milligram
mL	millilitre
mmol	millimole
sec	second
tlc	thin layer chromatography
TMS	tetramethylsilane

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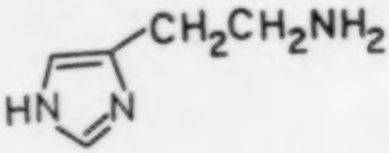
1.0.0.0.0 INTRODUCTION.

1.1.0.0.0 Pharmacological Effects of Histamine

Most body tissues contain low concentrations of histamine 1 in bound form which is produced by release from histidine by the action of histidine decarboxylase. Physical injury, the action of many chemical agents and antigen-antibody reactions can trigger the release of free histamine which exerts a potent pharmacologic effect on blood vessels, gastric secretion and bronchial smooth muscle. When the skin is injured the "triple response of Lewis"[1] which is characterized by localised redness followed by edema and then diffuse redness is often observed. Wasp and nettle stings cause itching and edema which has been attributed to histamine release. Histamine is also released in anaphylaxis and allergic diseases.

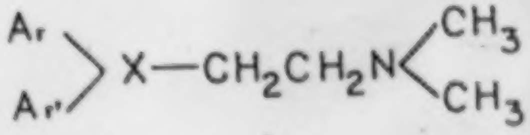


1

It is known that there are histamine H_1- and H_2-receptors. The interaction of histamine with histamine H_1-receptors is responsible for many allergic manifestations due to contraction of smooth muscle, dilation of blood vessels and stimulation of exocrine gland secretions whereas interaction with H_2-receptors causes stimulation of gastric acid secretion, relaxation of uterine smooth muscle and stimulation of isolated atria.[2]

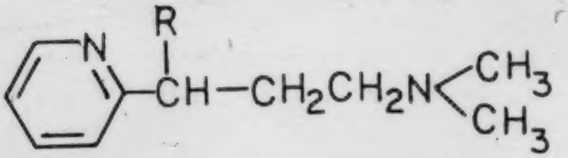
1.2.0.0.0 Histamine H_1-Receptor Antagonists.

Drugs which antagonize the action of histamine at histamine H_1-receptors are called histamine H_1-receptor antagonists. These drugs are frequently derivatives of ethylenediamine, ethanolamine and propylamine as illustrated by general structure 2 where Ar is

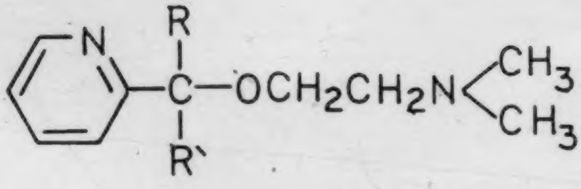


2

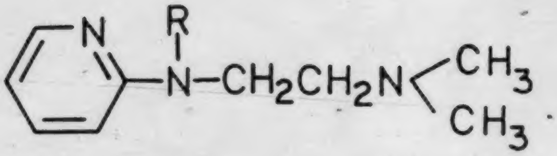
a phenyl group, Ar' is a phenyl, benzyl, pyridinyl, or thenyl group and X is N, O or C. 2-{α-[2-(Dimethylamino)ethyl]benzyl}pyridine (pheniramine) 3a, the halogenated derivatives bromopheniramine 3b and chloropheniramine 3c and their dextrorotatory enantiomers dexbrompheniramine and dexchlorpheniramine are derivatives of propylamine. 2-{p-Chloro-α-[2-(dimethylamino)ethoxy]benzyl}pyridine (carbinoxamine) 4a and 2-{α-[2-(dimethylamino)ethoxy]-α-methylbenzyl}pyridine(doxylamine) 4b are potent ethanolamine derivatives. 2-{Benzyl[2-(dimethylamino)ethyl]-amino}pyridine 5a (tripelennamine) and the derivatives halopyramine 5b and mepyramine (pyrilamine) 5c are ethylenediamine derivatives. Methapyrilene 5d, the thenyldiamine 5e and chlorothen 5f are structurally related antihistamines. Dimethindene 6 and triprolidine 7 are also clinically effective antihistaminics that possess a pyridinyl ring. The structure activity relationships for histamine H_1-receptor antagonists have been reviewed.[3] Histamine H_1-receptor antagonists are

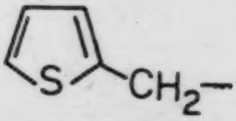
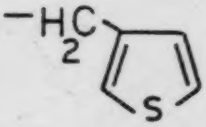
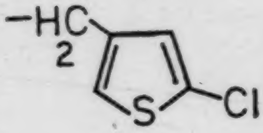


	R
3a	Ph
3b	4-Br-C_6H_4-
3c	4-Cl-C_6H_4-

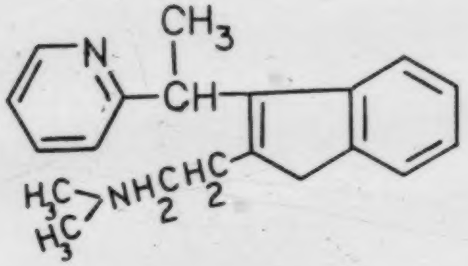


	R	R`
4a	H	4-Cl-C_6H_4-
4b	Me	Ph

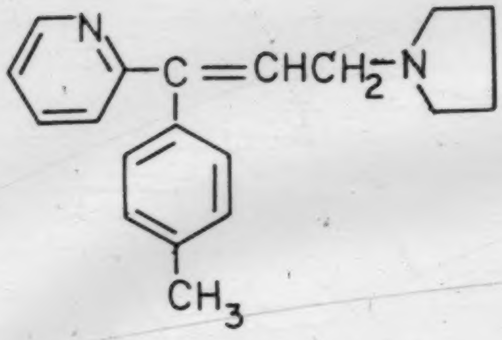


	R
5a	$-CH_2Ph$
5b	$4\text{-}Cl\text{-}C_6H_4\text{-}CH_2\text{-}$
5c	$4\text{-}MeO\text{-}C_6H_4\text{-}CH_2\text{-}$
5d	
5e	
5f	

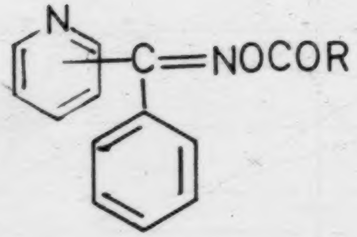
most effective for preventing the actions of histamine rather than reversing its action after the physiological response has been evoked. Histamine H_1-receptor antagonists are useful for the treatment of urticaria and hay fever but are of little benefit for the treatment of asthma.



6



7



8

In recent years there has been very little research directed toward the development of new histamine H_1-receptor antagonist possessing pyridinyl substituents. However Lee et al[4] reported a series of ketoximino esters of 2-, 3- and 4- benzoylpyridine oxime 8 that exhibited histamine H_1-receptor antagonist activity that was nearly devoid of anticholinergic effects. The propionyl analogs were the most active compounds.

1.3.0.0.0 Histamine H_2-Receptor Antagonists.

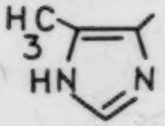
Drugs which antagonize the action of histamine at histamine H_2-receptors are called H_2-receptor antagonists. These drugs generally possess a heterocyclic ring containing a basic center, situated endocyclically or exocyclically, linked by a common side chain ($-CH_2SCH_2CH_2-$) to a polar hydrogen bonding group Y as illustrated by the formula 9. The Y moiety can be a thiourea 9a, a cyanoguanidine 9b, 9c and 9d, 1-nitro-2,2-diaminoethene 9e, 2-aminopyrimidine-4-one 9f or 1,2,5-thiadiazole-1-oxide 9g group.[5-11] It was also recently reported that a series of 4-(2-pyridinyl)butylisocytosines 10 exhibited both histamine H_1-and H_2-receptor antagonist activity.[12]

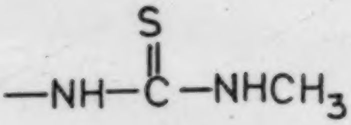
$\text{Het-CH}_2\text{-S-CH}_2\text{CH}_2\text{-Y}$

9

Het | Y

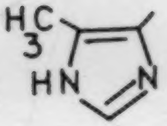
Metiamide 9a

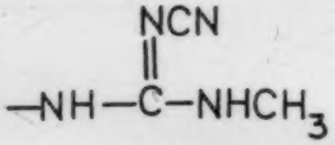




$-\text{NH}-\overset{\overset{\text{S}}{\|}}{\text{C}}-\text{NHCH}_3$

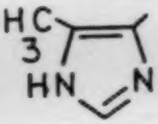
Cimetidine 9b

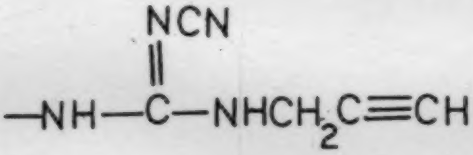




$-\text{NH}-\overset{\overset{\text{NCN}}{\|}}{\text{C}}-\text{NHCH}_3$

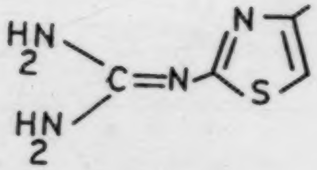
Etintidine 9c

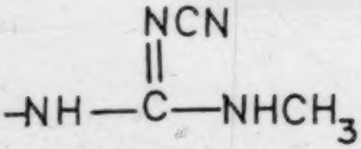




$-\text{NH}-\overset{\overset{\text{NCN}}{\|}}{\text{C}}-\text{NHCH}_2\text{C}\equiv\text{CH}$

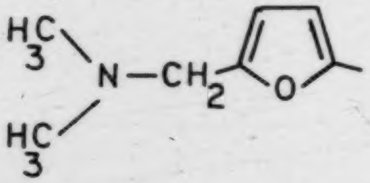
Tiotidine 9d

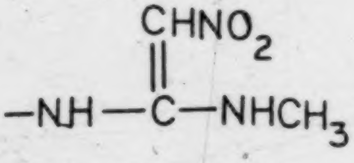

H2N
H2N
C=N
N
S



$-\text{NH}-\overset{\overset{\text{NCN}}{\|}}{\text{C}}-\text{NHCH}_3$

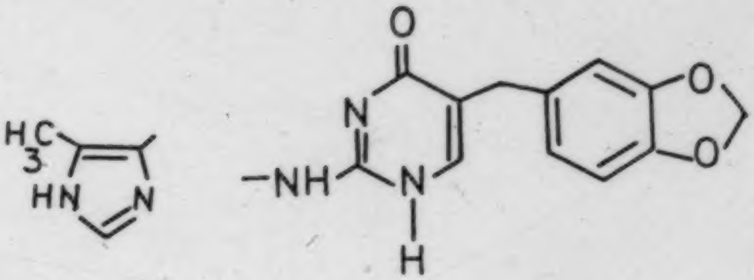
Ranitidine 9e


H3C
N—CH2
H3C
O

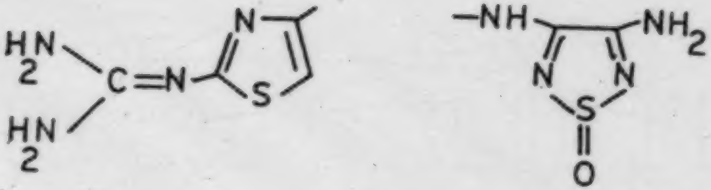


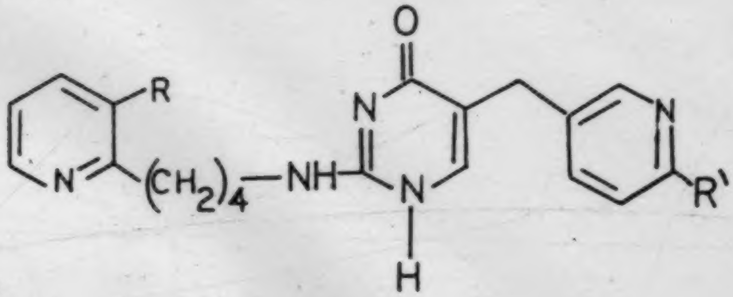
$-\text{NH}-\overset{\overset{\text{CHNO}_2}{\|}}{\text{C}}-\text{NHCH}_3$

Oxmetidine 9f



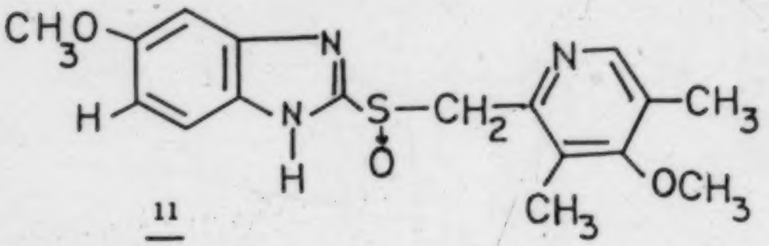
BL-6341A 9g





(SK&F 93319) 10 R=OMe R^1=Me

In duodenal ulcer patients omperazole 11 administered by the intragastric route inhibited acid secretion induced by sham feeding by a noncholinergic pathway without altering serum gastrin levels.[13]

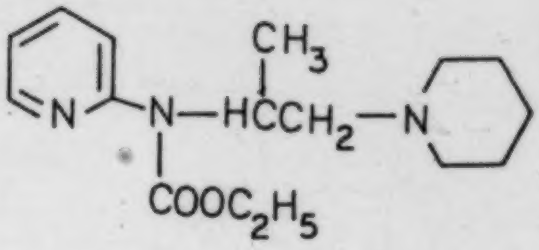


11

These results make it clear that the activity of H_2-antagonists varies with the nature of the aromatic heterocyclic ring (Het) and the moiety Y.[5-11] It is evident that H_2-antagonists interact with H_2-receptors in different ways. Clearly improved H_2-antagonists which are more selective and do not enter the central nervous system causing side effects, do not interact with β-adrenoceptors or cholinergic receptors, do not possess antiandrogenic activity, do not affect cytochrome P450 and have a longer duration of action are desirable.[14]

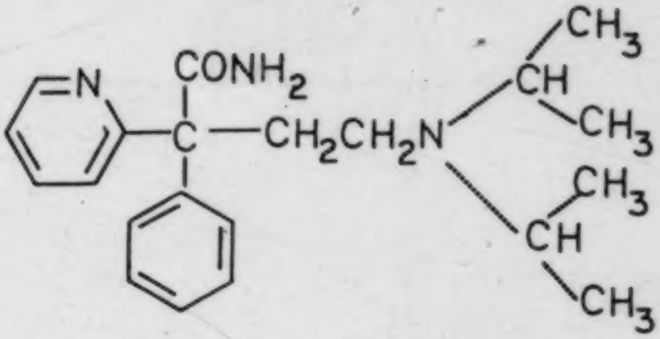
1.4.0.0.0 Pharmacologically Active Pyridines.

Many pyridinyl derivatives exhibit a pharmacological effect. It is not possible to review all active compounds since thousands of pyridinyl derivatives have been prepared and evaluated for pharmacological activity. The examples selected have been chosen to illustrate some of the more recent literature describing pharmacologically active pyridinyl compounds. Propiram 12 is a good example of analgesic agents which have a pyridinyl moiety.[15] Diisopyramide 13,[16] KB 1043 14[17] and



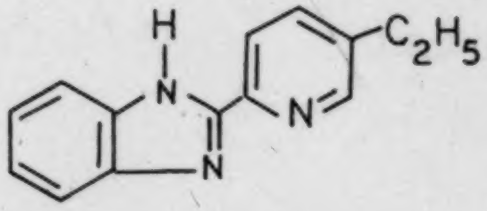
N
N—HCCH$_2$—N
CH$_3$
COOC$_2$H$_5$

12



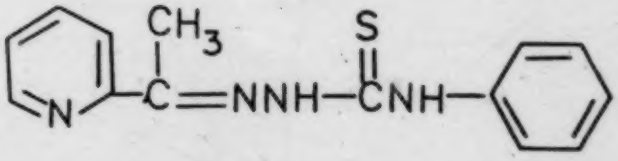
N
CONH$_2$
C
CH$_2$CH$_2$N
CH
CH$_3$
CH$_3$
CH
CH$_3$
CH$_3$

13



H
N
N
N
C$_2$H$_5$

14

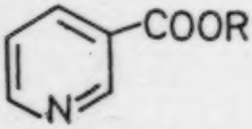


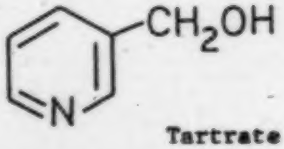
N
CH$_3$
C=NNH—CNH—
S

15

N-phenyl-2-[1-(2-pyridinyl)ethylidene]hydrazine carbothioamide 15[18] have been reported to exhibit antiarrhythmic, antiinflammatory and antimalarial activity respectively.

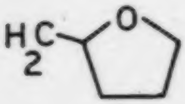
Nicotinic acid has been reported to be a weak peripheral vasodilator. This observation stimulated the synthesis of related compounds which included the methyl, isopropyl, benzyl and tetrahydrofurfuryl esters of nicotinic acid 16a-d[19-22] which exhibited vasodilating properties. Nicotinyl alcohol (3-pyridinylcarbinol) tartrate 17 is a commercially available vasodilator.



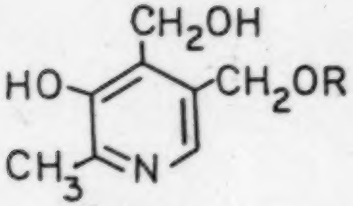


Tartrate

17

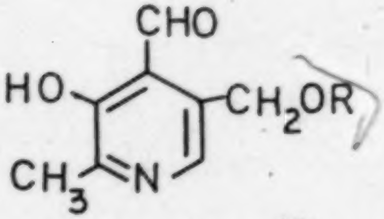
	R
16a	Me
16b	$CHMe_2$
16c	CH_2Ph
16d	

It had a longer duration of action relative to nicotinic acid and was active orally.[23,24] The chemistry and biochemical role of vitamin B$_6$ have been the subject of an excellent review.[25] Vitamin B$_6$ was originally thought to be a single substance viz, 4,5-di-(hydroxymethyl)-3-hydroxy-2-methylpyridine 18a commonly called pyridoxine or pyridoxol. Subsequent studies revealed that pyridoxine alone was not singularly responsible for all of the activity exhibited by the naturally occuring vitamin B$_6$. The related compounds pyridoxal 19a, pyridoxamine 20a and the 5-phosphates 18b, 19b, 20b were also active compounds.



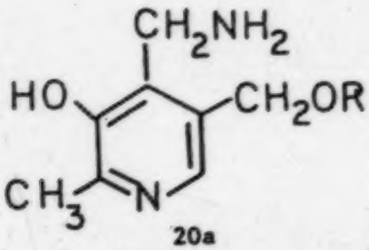
18a

18b



19a

19b



20a

20b

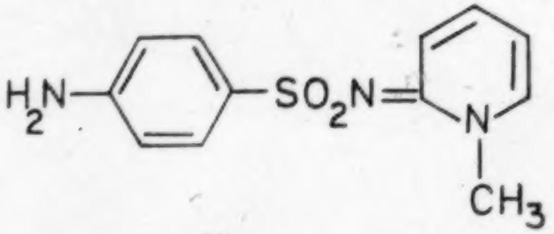
a, R=H

b, R=PO(OH)$_2$

In fact, pyridoxal phosphate is now recognized as being a coenzyme, called codecarboxylase which is implicated in the decarboxylation of a number of α-aminoacids including arginine, aspartic acid, glutamic acid, lysine, ornithine and tyrosine.[26,27]

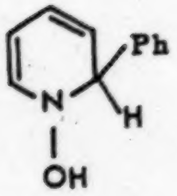
1.5.0.0.0 Pharmacologically Active 1,2-Dihydropyridines

Very few compounds possessing a 1,2-dihydropyridine ring system have been evaluated as pharmacological agents. Some dihydropyridines have been shown to be antibacterial agents. 1-Methyl-2-sulfanilimido-1,2-dihydropyridine 21 is one of the products obtained upon treatment of sulfapyridine with diazomethane. It is active as an antibacterial agent against *E. coli*[28].

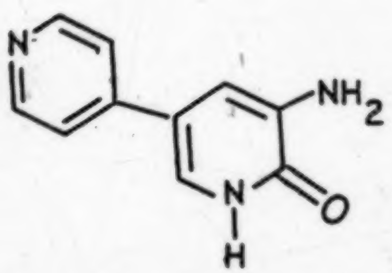


21

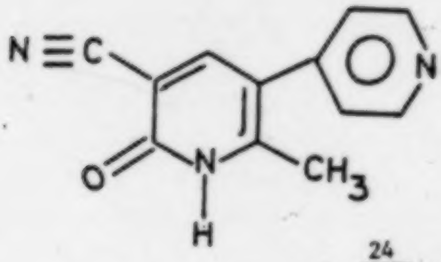
Reaction of pyridine-1-oxide with phenylmagnesium bromide gave 1-hydroxy-2-phenyl-1,2-dihydropyridine 22 which is a bactericide.[29] Amrinone 23[30] and an analog milrinone 24 are new dihydropyridine derivatives which act as inotropic and cardiotonic agents respectively.



22



23

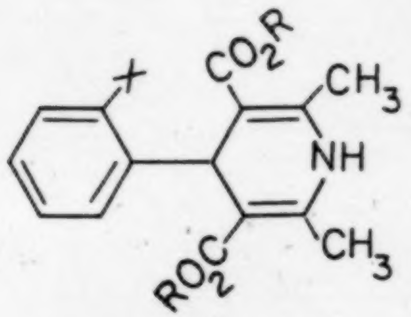


24

An extensive review describing pyridines and reduced pyridines with pharmacological activity has been published.[94]

1.6.0.0.0 Pharmacologically Active 1,4-Dihydropyridines

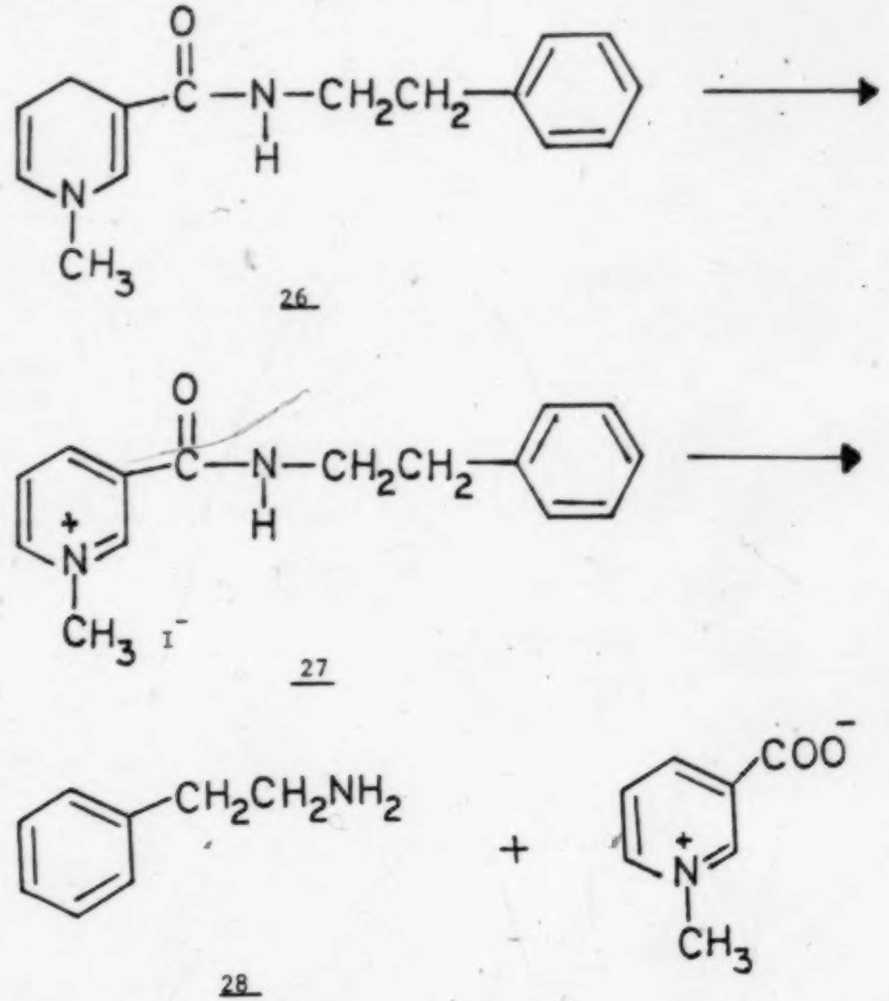
Several groups of investigators independently discovered that dihydropyridines obtained from the Hantzsch reaction are potent vasodilator hypotensives.[33] Nifedipine 25a is used as an antianginal and coronary dilator.[34] It dilates only peripheral vessels. Tachycardia can be prevented by the concurrent administration of a β-blocker. The related compound 25b SKF 24260, is being clinically evaluated for use in hypertension.[35] It also lowers blood pressure by selectively dilating peripheral vessels and causes tachycardia that may be prevented by administration of propranolol.



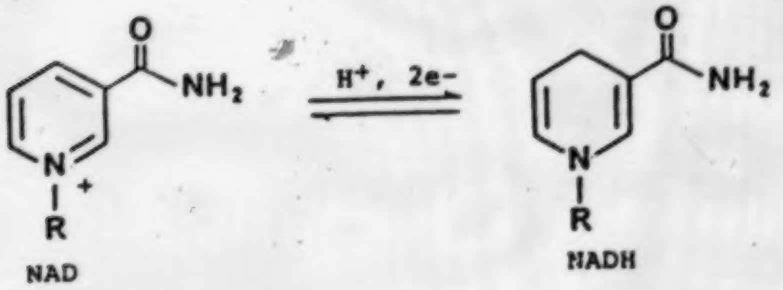
25a x = o -NO_2, R = CH_3

25b x = o -CF_3, R = CH_2CH_3

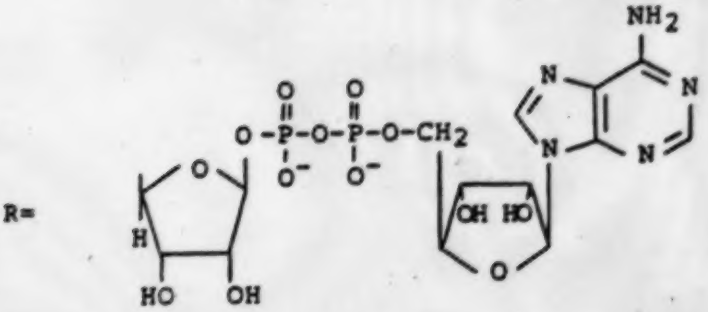
The dihydropyridine ⇌ pyridinium salt redox delivery system was successfully used for the specific delivery of phenylethylamine to brain using the dihydro derivative 26 to deliver the quaternary precursor 27 which "localized in" the brain to provide a sustained release form of phenyl ethylamine[36] 28.



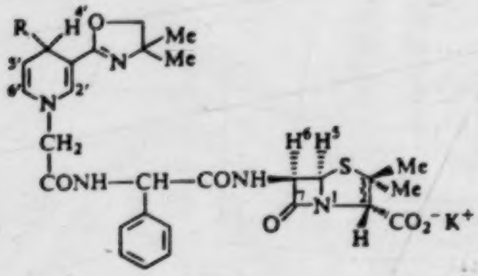
The recent interest in dihydropyridines can be traced to the reduced nicotinamide adenine dinucleotide (NADH) coenzyme 29$^{37-40}$ and the unique ability of this compound to reduce unsaturated functionalities such as carbonyls and conjugated olefins in biological systems. Thus, a considerable percentage of the current research in dihydropyridine chemistry is expended in synthesizing NADH mimics, exploring the reactions and mechanisms of these compounds, and utilizing these compounds in a variety of synthetic reactions.


NH2
H+, 2e-
NH2
N+
R
N
R
NAD
NADH

29


R=
NH2
N
N
N
N
O
O
O-P-O-P-O-CH2
O-
O-
O
H
HO
OH
OH HO
O

The 1,4-dihydropyridylacetic acid 30 exhibited moderate antibacterial activity toward Gram-positive strains.[41]


R
H
O
Me
Me
N
N
CH₂
CONH—CH—CONH
H
H
S
Me
Me
O
N
H
CO₂⁻ K⁺

30

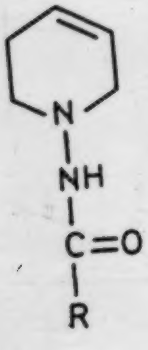
a, R = Ph

b, R = Me

c, R = M-Bu

1.7.0.0.0 Pharmacologically Active Tetrahydropyridines

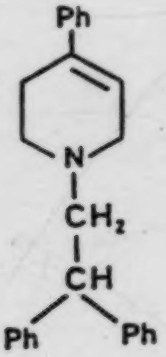
Very few tetrahydropyridines have been examined relative to the number of piperidines which have been evaluated pharmacologically. Those which have the greatest attention are derivatives of 1,2,5,6-



R = alkyl or phenyl

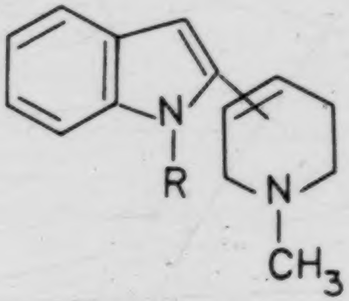
31

(or 1,2,3,6-)tetrahydropyridine. Many of these are potent hypotensive agents, a limited number are analgesics and some possess both properties. Compounds which include the N-carbonylamino-1,2,3,6-tetrahydropyridine moiety 31 and N-substituted-4-phenyl-1,2,5,6-tetrahydropyridinyl moiety 32 have been reported to possess analgesic activity.[42,43]



32

During an investigation of 2-tetrahydropyridinyl indoles 33 as intermediates in the synthesis of certain model indole alkaloid systems it was found that a few of these compounds exhibited antihistaminic and antiserotonin activity.[44]

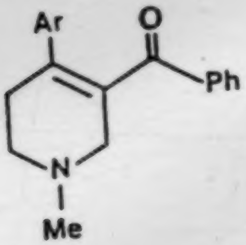


R = H

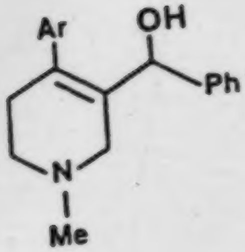
= $CH_2C_6H_5$

33

Some derivatives of 5- benzoyl-1-methyl-4-aryl-1,2,3,6-tetrahydropyridine 34 and their alcohol reduction products 35 have been tested for pharmacological activity. The ketones 34 were found to be useful antipyretic and antiinflammatory agents whereas the alcohols 35 possessed diuretic properties.[45,46]



34

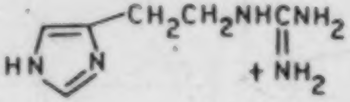
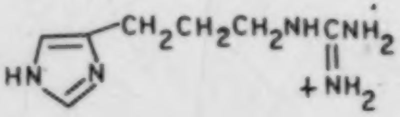
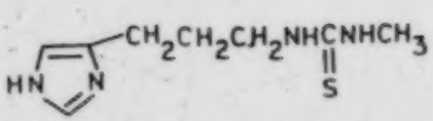


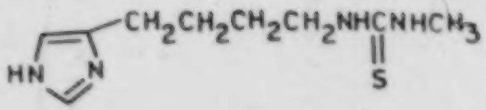
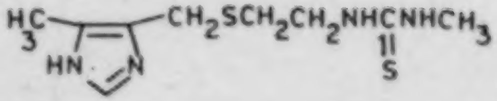
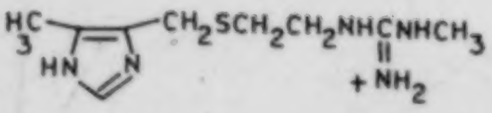
35

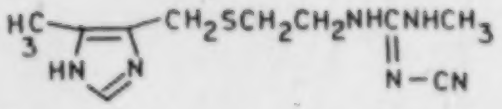
1.8.0.0.0 Structure-Activity Relationships for Histamine H_2-Receptor Antagonists.

Histamine H_2-receptor antagonists are a new class of compounds. It would be premature at this time to make definite conclusions regarding structure-activity correlations. Furthermore the perception of such structure-activity correlations depends on the manner in which the study was analysed. Current concepts[47] regarding which structural features of these antagonists may be important in explaining their potencies have been developed from results obtained during the development of cimetidine analogs. The summary in Table 1 indicates some of the results that were used in the development of improved H_2-receptor antagonists. Special consideration was given to the chemistry of the imidazole ring, to incorporating groups in place of the ammonium group of histamine and to the length of the alkyl side chain. These initial results provided valuable information regarding the structural requirements for H_2-receptor antagonist activity. However other structural variations could provide longer acting drugs having a greater potency. Although these H_2-receptor antagonists all possess an imidazole ring, other heteroaromatic rings may be equally effective. However it is clear that the tautomeric species present at physiological pH is relevant to H_2-receptor antagonist activity for those compounds possessing an imidazole ring. One must also consider the chemical features of the basic group which replaces the side chain nitrogen of histamine and the effects resulting from alteration of the side chain. The H_2-receptor antagonists shown in Table 1 act as competitive antagonists of histamine, the effect is reversible and the H_2-antagonists are readily displaced from *in vitro* preparations by changing the bath fluid. These compounds appear to have a relatively short duration of action *in vivo*. These H_2-antagonists do not interact irreversibly with or bind covalently to the H_2-receptor. It is likely that these H_2-antagonists form a reversible association complex with the H_2-receptor. The concept of receptor-site occupancy can be used to identify chemical features common to these competitive H_2-antagonists to obtain information regarding the chemical binding sites. Thus one could envisage the imidazole ring of histamine engaging the same specific site on the H_2-receptor as the imidazole ring of the H_2-antagonist. Histamine having a C-4 methyl substituent acts as an H_2-receptor agonist. The incorporation of a 4-methyl substituent into the imidazole ring of H_2-antagonists improved activity since it increased the population of the N^{τ}-tautomer which is thought to be the active tautomeric species at the H_2-receptor. Methylation at the C-2 position of histamine reduced H_2-agonist activity at H_2-receptors. The incorporation of a C-2 methyl substituent into the imidazole ring of metiamide also reduced H_2-antagonist activity. It should be pointed out that agonist compounds interact with the H_2-receptor and also elicit a receptor response viz, H_2-agonists possess "efficacy" or "intrinsic activity". On the other hand, H_2-antagonists interact with the H_2-receptor but exhibit no "intrinsic" response. Thus some heterocyclic analogs of histamine exhibit weak H_2-agonist activity[48] wheareas others as burimamide, metiamide and cimetidine may be active H_2-receptor antagonists.[49] These observations are consistent with the initial postulate that the imidazole ring of the H_2-antagonist also binds to the receptor. However only some of the chemical properties of the ring need to be retained for H_2-antagonist selectivity. If the heterocyclic ring of the H_2-antagonist binds to the receptor site that would otherwise accommodate the imidazole ring of histamine, then the rest of the H_2-antagonist molecule could contribute additional binding by interacting with some accessory region of the H_2-receptor. The molecular structure of the H_2-antagonist appears to be quite critical to H_2-antagonist activity. Histamine H_2-antagonistic effects are markedly influenced by altering the length of the side chain. This suggests that the thioureido or guanidino moieties may provide additional co-operative binding to the H_2-receptor. There are a number of speculative mechanisms by which the thioureido and guanidino moieties may contribute to additional binding to the H_2-receptor.

Table 1. Some Key Compounds Prepared in the Development of Histamine H_2-Receptor Antagonists

Compound	Structure	Antagonist Activity In Vitro K_B,[a] 10^{-6}M	In Vivo ID_{50},[b] µmol/kg
36. N^{α}-Guanylhistamine: The "lead", a weakly active partial agonist		130	800
37. SK&F 91486: Lengthening the side chain increased activity		22	100
38. SK&F 91581: Thiourea analog is much less active as an antagonist but is not an agonist		115[c]	d

39, Burimamide: Lengthening the side chain dramatically increased antagonist activity		7.8	6.1
40, Metiamide: Introducing -S- into the side chain and CH_3 into the ring altered imidazole tautomerism and increased activity		0.92	1.6
41, Guanidino isostere: Replacing C=S by C=NH afforded a basic side chain and reduced activity		16	12

42, Cimetidine:Introducing a CN substituent reduced basicity and increased activity		0.79	1.4

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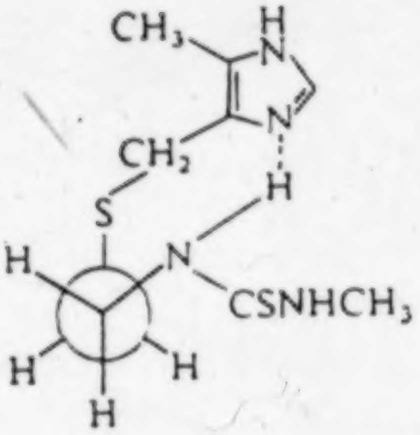
a Dissociation constant K_B, determined *in vitro* on guinea pig right atrium against histamine stimulation.

b Activity *in vivo* as an antagonist of near maximal histamine stimulated gastric acid secretion in anesthetised rat using a lumen perfused preparation. The ID_{50} is the intravenous dose required to produce 50% of inhibition.

c Refined data

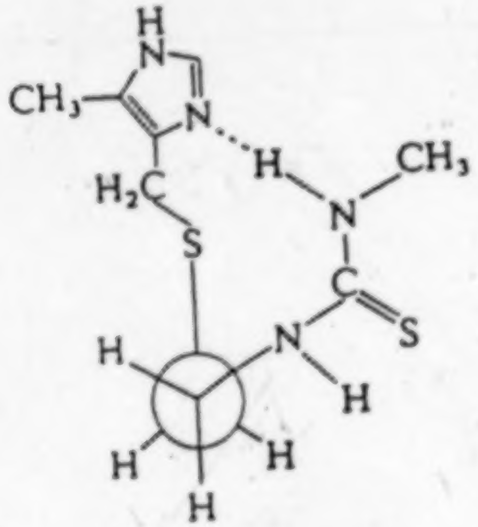
d No antagonism observed up to an intravenous dose of 256 umol/kg.

For example, these moieties could interact with a specific molecular site on the H_2-receptor via hydrogen bonding or by acting as an electron-pair donor in metal complexation.[50,51] The thioureido and guanidino moieties, which are highly polarizable and planar, could also participate in a "stacking interaction" of the type proposed for nucleotide bases.[52,53] Since burimamide, metiamide and cimetidine are hydrophilic molecules, it is unlikely that hydrophobic binding constitutes a major contribution to the drug-receptor interaction. On the other hand several other receptor antagonists such as α- and β-adrenergic blocking agents, anticholinergics and histamine H_1-receptor antagonists possess lipophilic substituents in which case hydrophobic interactions are relevant to the drug-receptor interaction.[54] The correlation between chain length and H_2-receptor antagonist activity poses the question as to whether a particular side chain conformer may be relevant to H_2-antagonist activity. The overall molecular conformation of the H_2-antagonist molecule is determined by the alkyl(methylthioethyl)side chain. ^1H nmr studies for metiamide and cimetidine in CD_3OD solution indicated that the ethane moiety($-CH_2CH_2-$) present in the side chain is probably a statistical mixture of gauche and trans conformers where 33% of the metiamide molecules assumed the trans conformation at any give time (cf Figure 1).[55] Infrared spectroscopic studies using bromoform as solvent indicated that mixtures of inter- and intramolecular hydrogen bonded species were present.[56] The intramolecular interaction for the thioureido derivatives involved the thiourea NH group and the imidazole basic nitrogen atom hydrogen bonded in a ring. Examination of Corey-Pauling-Koltum (CPK) space filling molecular models indicated that eight or ten membered intramolecular hydrogen bonded rings are possible. For metiamide, the 8-membered ring illustrated by 43 possessed a gauche conformation about the $-CH_2CH_2-$ bond (Figure 1), without restricting the thiourea configuration. On the other hand the 10-membered ring requires an E,Z configuration for the thiourea group which can accommodate either gauche 44 or trans 45 conformations about the $-CH_2CH_2-$ bond.



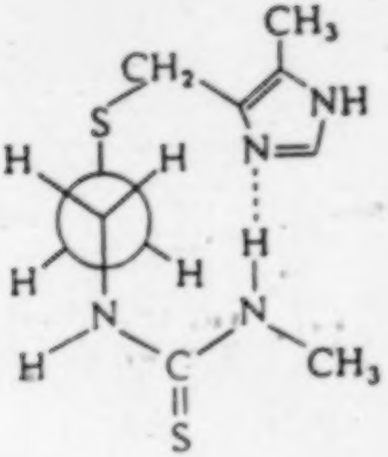
43

Eight-membered ring, $-CH_2CH_2$-gauche, imidazole in N^{τ}-H tautomer, thiourea group not constrained.



44

Ten-membered ring, $-CH_2CH_2-$ gauche, imidazole in N^{τ}-H tautomer, thiourea group in E,Z configuration.



45

Ten-membered ring, -CH_2CH_2-trans, imidazole in N^{τ}-H tautomer thiourea group in E,Z configuration as found in the crystal.

Figure 1. Intramolecular hydrogen-bonded structures for metiamide (viewed as Newman projection structures along the CH_2CH_2- bond).

The conformation of cimetidine is similar except the cyanoguanidine group assumes an E,Z configuration. The X-ray crystal structure of these antagonists has also been studied. Burimamide molecules are linked together by a complex network of hydrogen bonds between the imidazole rings (NH---N), and the thiourea residues (NH-----S) although there are no thiourea imidazole contacts.[58] The alkyl chain is extended, approximately planar and the thiourea group is in the staggered E,Z conformation (Figure 2).

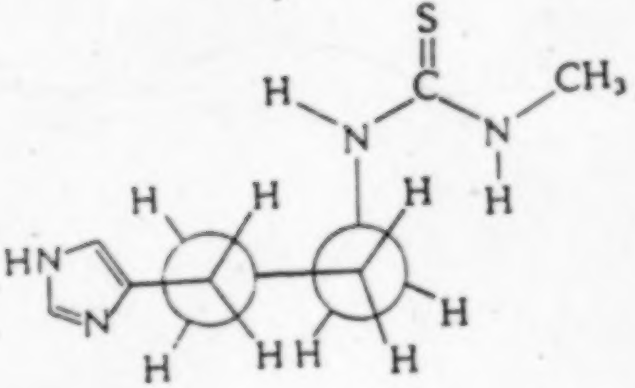


Figure 2. Structure of a single molecule of burimamide[58] showing imidazole in N^{τ}-H tautomer; $(CH_2)_4$ groups in respectively, trans, trans and half-gauche conformations and the thiourea group in the E,Z configuration.

The crystal structures for metiamide and thiaburimamide differ from that of burimamide.[57] These molecules are folded rather than extended as is the case for burimamide. There is an intramolecular NH----N hydrogen bond between a thiourea NH and the imidazole $\overset{\pi}{N}$-atom forming a 10-membered ring in which the -CH_2CH_2- bond possesses a trans conformation 45 as illustrated in Figure 1. The thiourea groups exist in the staggered E,Z configuration like burimamide and form hydrogen bonded pairs linked via N-H----S bonds. The molecular conformation of cimetidine is very similar to that adopted by metiamide and thiaburimamide and a 10-membered hydrogen bonded ring is formed by an intramolecular NH---H hydrogen bond between a cyanoguanidine NH and the imidazole $\overset{\pi}{N}$-atom as illustrated in Figure 3.[59] The crystal structure of cimetidine is quite similar to that of metiamide. The cyanoguanidine groups exist in an E,Z configuration and the lone electron pair on the imino nitrogen formed a N-H----N hydrogen bond between pairs of cyanoguanidine groups giving rise to a 12-membered ring. This closely resembled the 8-membered rings present for metiamide.

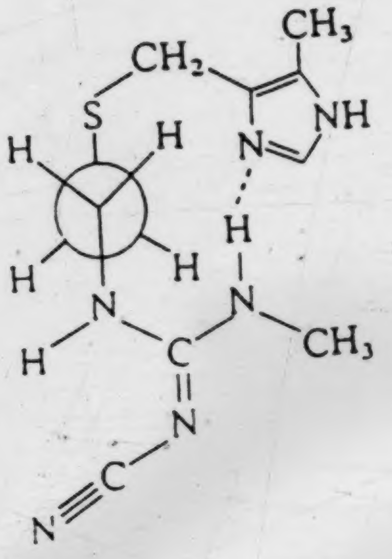

CH₃
CH₂
S
H
H
NH
N
H
H
H
H
N
N
H
C
CH₃
N
C
N

Figure 3. Structure of a single molecule of cimetidine[59] showing an intramolecular hydrogen bonded 10-membered ring, $-CH_2CH_2-$trans, imidazole in N^{τ}-H tautomer and the cyanoguanidine group in the E,Z configuration.

These results provided further evidence for isosterism between the thiourea and cyanoguanidine moieties. An interesting correlation between the crystal structure and crystal stability has also been demonstrated for these compounds where stability correlated with increasing melting point and reduced aqueous solubility as illustrated in Table 2.[57] Replacement of a CH_2 moiety in the side chain of burimamide by sulfur was initially performed to effect an isosteric substitution which would modify the electronic properties of the side chain slightly and increase conformational flexibility.[60] It also increased the population of active N^{τ}-tautomer of histamine as shown in Figure 4. It was also found that 4-methylhistamine was much more active on the atrium (43% of histamine) than on the ileum (0.23%) suggesting the C-4 methyl substituent increased the population of N^{τ}-tautomer.

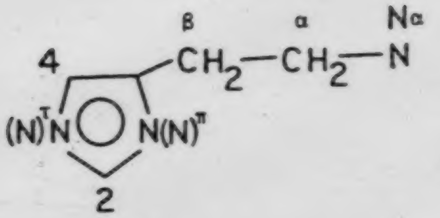
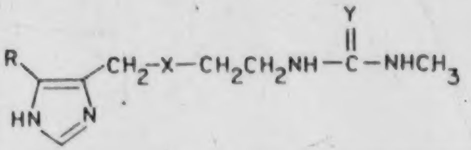


Figure 4. Histamine numbering according to Black and Ganellin.[47]

Table 2. Physical Characteristics of Crystalline Burimamide, Metiamide, Cimetidine and Related Compounds.[57]



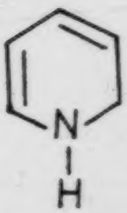
Compound	R	X	Y	mp, °C	Intra-molecular Hydrogen Bonding	Aqueous Solubility g/L	Aqueous Solubility M
Metiamide	CH_3	S	S	150-152	Yes	3.2	0.013
Cimetidine	CH_3	S	NCN	141-142	Yes	11.4	0.045
Burimamide	H	CH_2	S	129-130	No	14.7	0.069
Methylburimamide	CH_3	CH_2	S	110-112	No[a]	25.4	0.112
Thiaburimamide	H	S	S	96-98	Yes	70.4	0.306

[a] The absence of intramolecular hydrogen bonding is inferred from the solid state infrared spectrum for methylburimamide.[57]

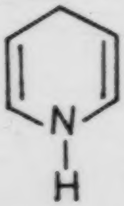
The crystal structures provided evidence for the presence of a cyclic intramolecular hydrogen bonded conformation in these compounds with a thioether side chain. It is interesting that a 10-membered ring should exist and one must consider if it contributes to the greater activity of these molecules. It is not known whether it requires this configuration for biological activity or whether the thioether link simply functioned to increase molecular flexability in a way that is biologically advantageous. Thus, in addition to electronic effects, it is possible that conformational effects of the thioether linkage also contributed to the activity of these compounds as histamine H_2-receptor antagonists.

1.9.0.0.0 The Chemistry of 1,2-Dihydropyridines

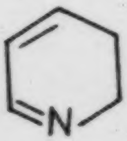
In theory, there are five isomeric dihydropyridines 46-50. However most of the known dihydropyridines have either the 1,2-dihydro structure 46 or the 1,4-dihydro structure 47. The reason why 46 and 47 are more common than the others is due to the involvement



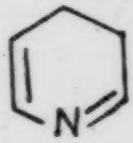
46



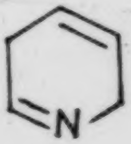
47



48



49



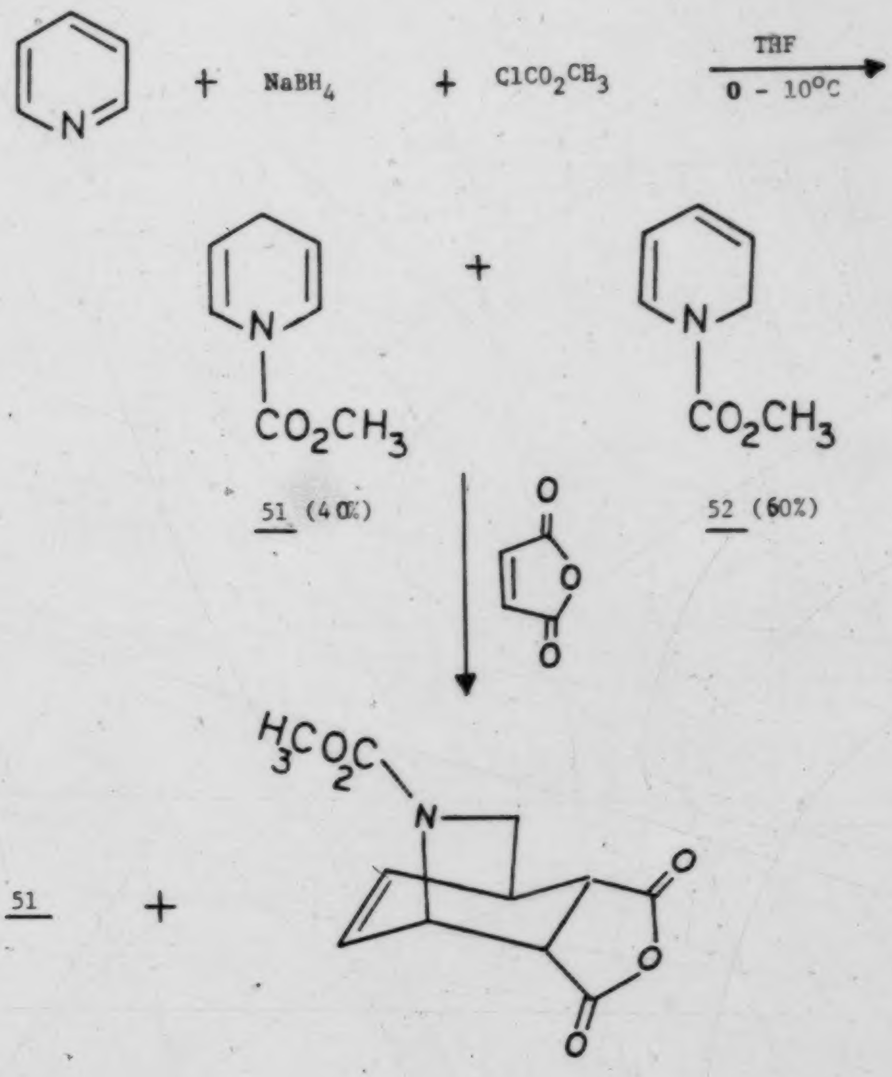
50

of the nitrogen lone pair in the π electron system of the former. The isomers 46 and 47 have the highest number of sp^2 hybridized centers. Strong nucleophiles reacted preferentially at the C-2 position of pyridine whereas substituted pyridines often undergo C-4 substitution. Weak nucleophiles usually attack the C-4 position of pyridine.[61] The following discussion will provide a general view to the structure, synthesis, physical and chemical properties of 1,2-dihydropyridines with particular emphasis on those aspects pertinent to the thesis.

1.9.1.0.0 Synthesis of 1,2-Dihydropyridines

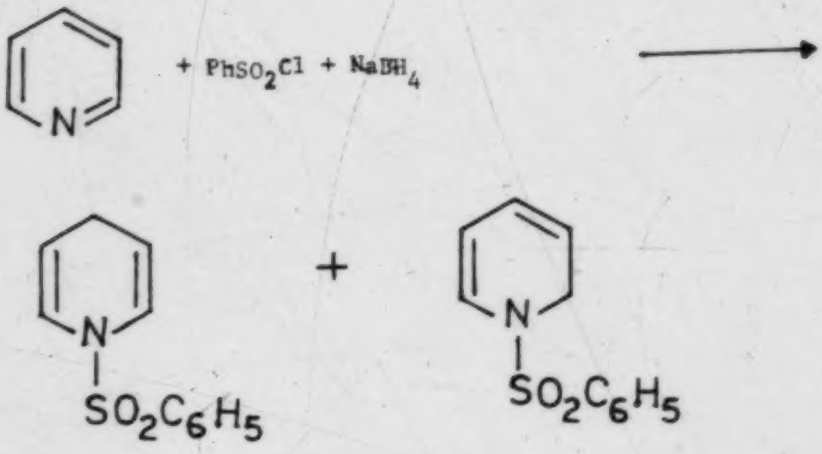
1.9.1.1.0 Synthesis of 1,2-Dihydropyridines by Nucleophilic Addition of Metal Hydrides

A number of dihydropyridine derivatives have been prepared by reduction of the corresponding pyridines or pyridinium salts with complex metal hydrides.[62,63] When pyridine is treated with sodium borohydride in the presence of methyl chloroformate in tetrahydrofuran below 10°C, a mixture containing 40% of the 1,4-isomer 51 and 60% of the 1,2-isomer 52 is obtained. The 1,2-isomer 52 can be removed by treating the mixture with maleic anhydride and washing with 15% sodium hydroxide, which removes the Diels-Alder adduct 53. The 1,4 isomer is not produced when the reaction is carried out in methanol at -65°C.


+ NaBH4 + ClCO2CH3
THF
0 - 10°C
CO2CH3
+
CO2CH3
51 (40%)
52 (60%)
51 +
H3CO2C
O
O

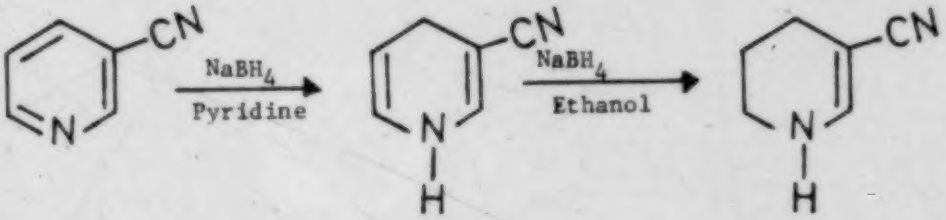
53

The temperature dependent ratio of products appears to be general since Knaus[64] found that the reaction of benzenesulfonyl chloride with pyridine, as both solvent and reactant, in the presence of sodium borohydride at 25°C afforded the 1,4-isomer 54 and the 1,2-isomer 55 in a ratio of 5:4. When the reaction was performed at -65°C the respective ratio was 1:8.



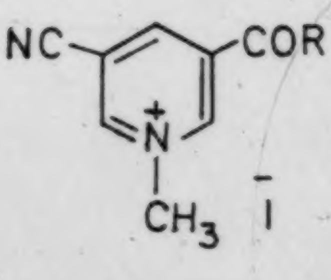
54 55

Sodium borohydride reduces pyridines with electron withdrawing substituents in the 3-position, or, better, in the C-3 and C-5 positions, to dihydropyridines.[65-67] Thus, 3-cyanopyridine was reduced[67] to the corresponding 1,4-dihydropyridine 57 in aprotic solvents but to the tetrahydropyridine 58 in ethanol as illustrated below.

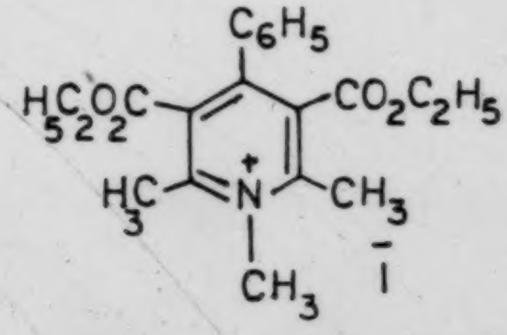

CN
NaBH$_4$
Pyridine
N
CN
NaBH$_4$
Ethanol
N
H
CN
N
H

56 57 58

Sodium borohydride reduction of the unsymmetrically substituted pyridinium salts 59a-b gave a mixture of the corresponding 1,2-, 1,4- and 1,6-dihydropyridines.[68] Lithium aluminum hydride reduction of 60 is reported[69] to yield 1,2-dihydropyridines. Similar results were also obtained for alkylpyridinium salts.[70,71]


NC
COR
N
+
CH$_3$
I
-

59


C$_6$H$_5$
H$_5$C$_2$O$_2$C
CO$_2$C$_2$H$_5$
H$_3$C
N
+
CH$_3$
CH$_3$
I
-

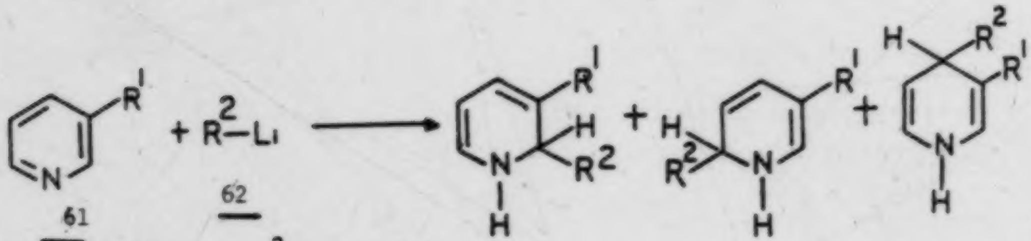
a, R = OEt

60

b, R = NH$_2$

1.9.1.2.0 Synthesis of 1,2-Dihydropyridines by Nucleophilic Addition of Organometallic Reagents

Dihydropyridines have been prepared by the reaction of organometallic reagents with pyridines, pyridine-1-oxides or pyridinium salts. Reaction of 3-substituted pyridines 61 with an alkyl lithium 62 afforded mixtures of 1,2-, 1,6- and 1,4-dihydropyridines 63, 64, and 65 respectively.[72]

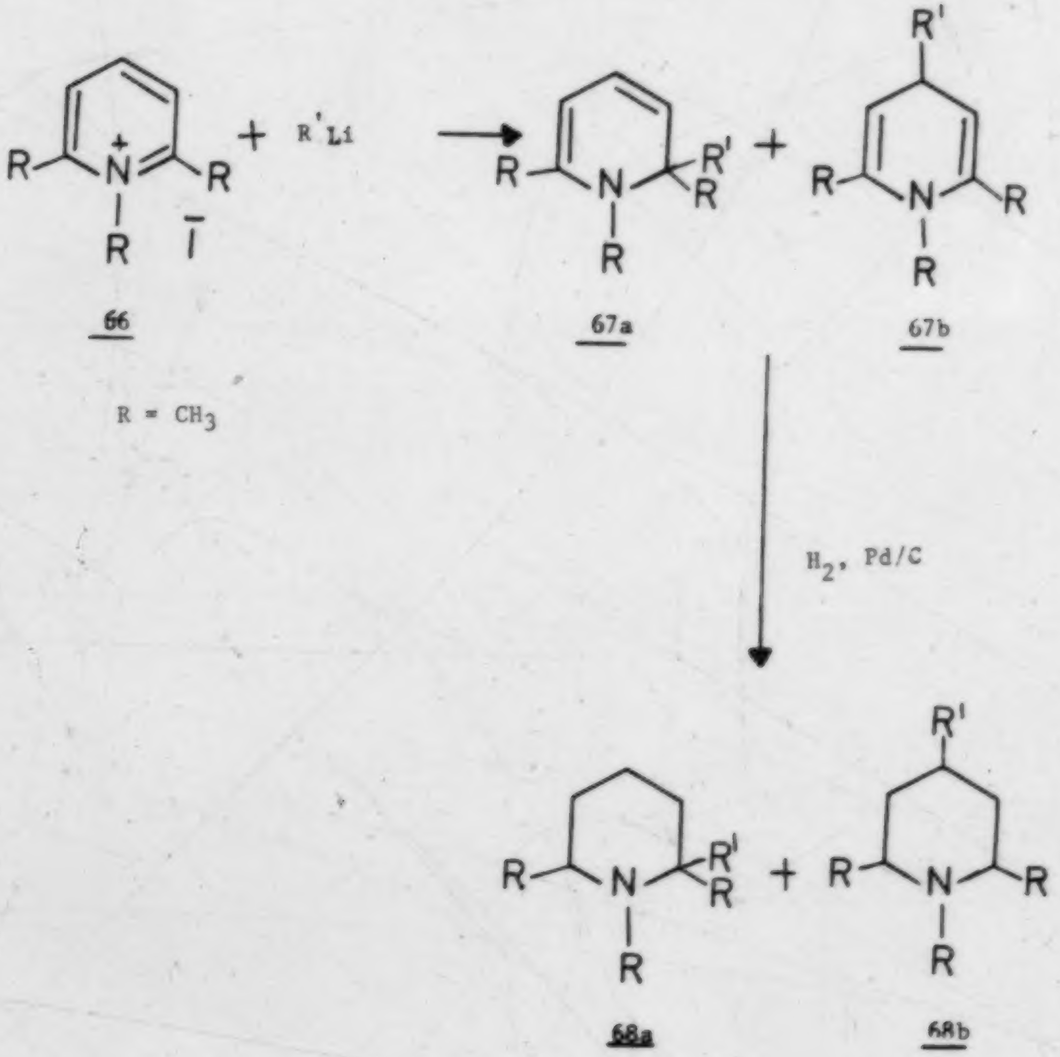


61 62

R^1=CN, CO_2Me, $CONEt_2$ R^2=t-Bu, n-Bu

63 64 65

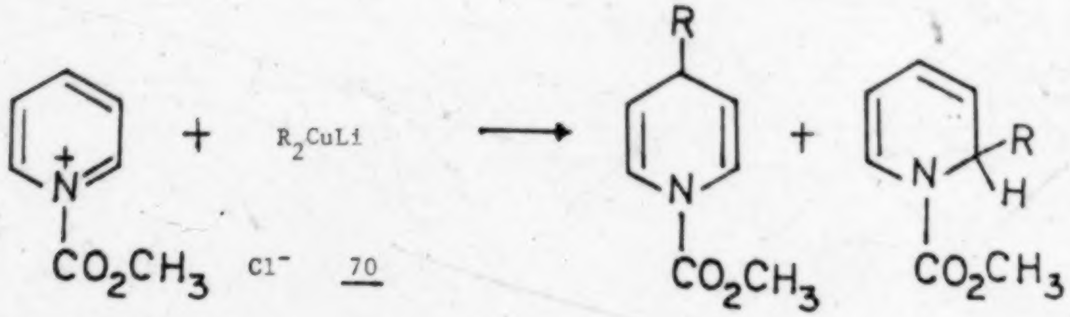
alkyllithium reagents react with pyridinium salts to give low yields of the highly reactive alkyldihydropyridines 67, which were characterized as the piperidines 68. Phenyllithium and tert-butyllithium, however gave exclusively the 1,2-isomer 67a in good yield.[73]


R'Li
66
67a
67b
H$_2$, Pd/C
68a
68b

R = CH_3

For R'=Ph,$C(CH_3)_3$	67a 41-80%	67b 0%
For R'=C_3H_7;n-Bu	68a 23-32%	68b 7-8%

Lithium organocuprates have been reported to add predominantly at the 4-position of pyridinium salts to give high yields of 1,4-dihydropyridines together with small amounts of the 1,2-isomers[74] as illustrated below.



69

56-86%

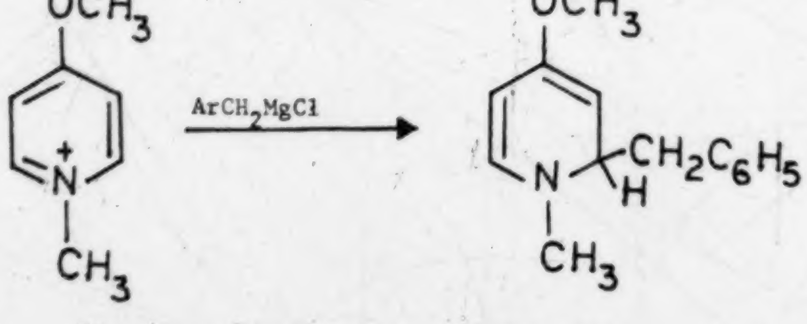
2-8%

R = alkyl,aryl

71

72

4-Methoxy-1-methylpyridinium iodide 73 reacted with Grignard reagents to give the unstable 1,2-dihydropyridines 74[75]



73

74

1.9.2.0.0 Physical Properties of 1,2-Dihydropyridines

1.9.2.1.0 Electronic Structure of 1,2-Dihydropyridines

The nitrogen lone pair and the electrons of the two double bonds in the 1,2-dihydropyridine ring system are localized as confirmed by molecular orbital calculations. However, if an electron attracting substituent is present at C-3 and/or C-5 substantial delocalization takes place.[76]

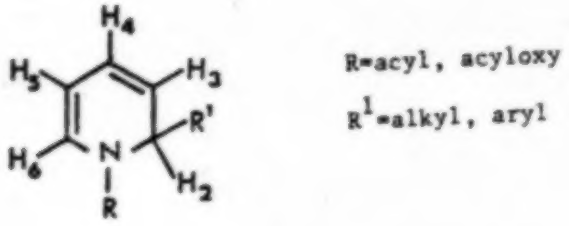
1.9.2.2.0 Infrared Spectra of 1,2-Dihydropyridines

Correlation of the dihydropyridine structure with absorption maxima in the ir region has not been developed to any great extent. However, dihydropyridines give rise to two stretching vibrations of medium to strong intensity due to the dienamine system which appear in the 1520-1640 cm^{-1} region.[77,78,79]

All N-unsubstituted dihydropyridines absorb in the 3100-3500 cm^{-1} region and show the characteristic stretching frequencies for bonded and non bonded NH groups.[80] The number and position of these depend on structural factors and on the condition of measurement.

1.9.2.3.0 Proton Magnetic Resonance Spectra of 1,2-Dihydropyridines

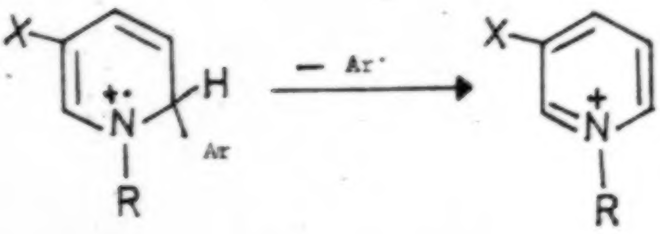
Nuclear magnetic resonance is a valuable spectroscopic method for identification of dihydropyridines. The chemical shift positions of the ring protons range from δ 4.2 to 6.75 and usually H-6>H-4>H-3>H-5>H-2.[81,82] If the ring is substituted the multiplicity of the signals is dependent upon the substituents' position. Typical J values (Hz) for compound 75 are $J_{2,3}$=4, $J_{3,4}$=8, $J_{4,5}$= 5.5 and $J_{5,6}$=6.[76]


H4
H5
H3
R'
H6
N
H2
R
R=acyl, acyloxy
R1=alkyl, aryl

75

1.9.2.4.0 Mass Spectra of 1,2-Dihydropyridines

In recent years mass spectrometry has been used occasionally for the structural elucidation of dihydropyridines.[83,84] Substituted 2-aryl-1,2-dihydropyridines 76 preferentially lose an aryl radical[85,86] to give the pyridinium ion 77 as illustrated below.


X
H
N
Ar
R
— Ar·
X
N
R

76

77

X = CN or $CONH_2$

Other less important fragmentations include the loss of the N-alkyl substituent[85,86], cleavage of the C-3 and/or C-5 substituent, and opening of the heterocyclic ring.

1.9.3.0.0 Chemical Properties of 1,2-Dihydropyridines

1.9.3.1.0 Stability of 1,2-Dihydropyridines

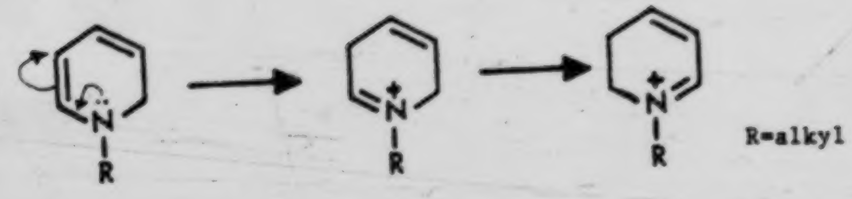
Recent studies indicated that N-methyl-1,4-dihydropyridine was more stable than the corresponding 1,2-isomer.[87] The stability of 1,2-dihydropyridines increases if the substituents at the N-1, C-3 and/or C-5 positions are electron withdrawing substituents which are capable of resonance interaction with the dienamine system of 1,2-dihydropyridine.

1.9.3.2.0 Electrophilic Addition to Ring Carbon

Dihydropyridines in most cases form vinyl carbanions upon reaction with strong metalating agents and these accordingly react with electrophiles. For example, 3-cyano-1,2-dihydropyridines react with lithium diisopropylamide (LDA) to afford 2-lithio-1,2-dihydropyridine which upon quenching with deuterium oxide yield the deuterated dihydropyridines.[88]

1.9.3.3.0 Acid-Base Properties of 1,2-Dihydropyridines

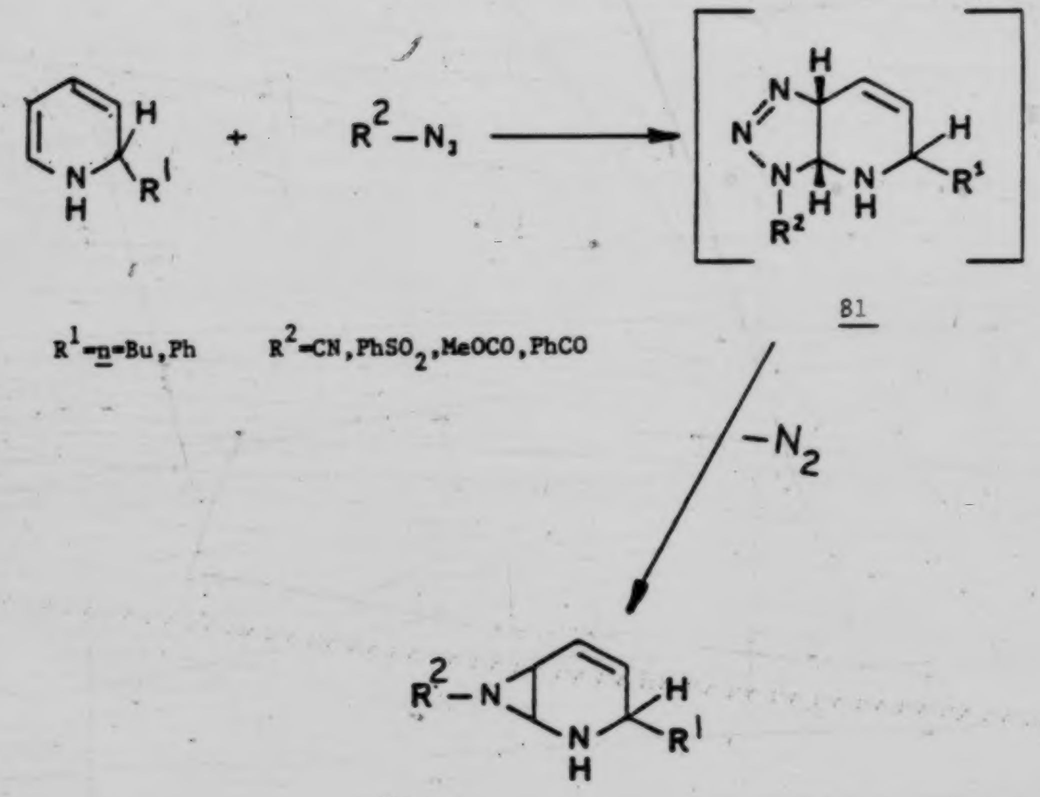
In a pioneering study,[89,90] it was shown that mild acid treatment of dihydropyridines 78 afforded the iminium salt 79 which can isomerize to 80.



78 79 80

1.9.3.4.0 1,3-Dipolar Cycloaddition Reactions of Enamines with Organic Azides

1,2-Dihydropyridines react as enamines with azides via a 1,3-dipolar cycloaddition reaction to yield the bicyclic intermediates 81 that expel nitrogen and afford the diazabicycloheptenes 82.[91]


H
R¹
N
H
+
R²—N₃
H
N
N
N
H
N
H
H
R¹
R²
−N₂
R²—N
H
N
H
R¹

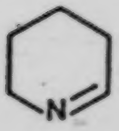
81

R^1=n-Bu,Ph R^2=CN,$PhSO_2$,MeOCO,PhCO

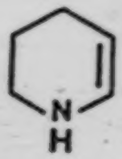
82

1.10.0.0.0 1,2,3,6 - Tetrahydropyridines

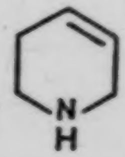
The dehydrogenation of piperidine and saturation of two of the double bonds of pyridine can give one of three isomeric tetrahydropyridines, viz 2,3,4,5-tetrahydropyridine (1-piperideine) 83, 1,2,3,4-tetrahydropyridine (2-piperideine) 84 and 1,2,3,6-tetrahydropyridine (3-piperideine) 85.



83



84



85

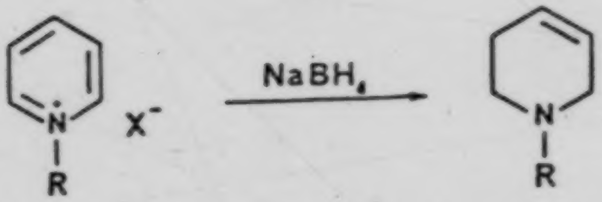
1,2,3,6-Tetrahydropyridine 85 is the only isomer that is stable as the free base. Excellent reviews describing the chemistry and pharmacology of 1,2,3,6-tetrahydropyridines have been published.[92-95]

1.10.1.0.0 Synthesis of 1,2,3,6-Tetrahydropyridines

1,2,3,6-Tetrahydropyridines have been synthesized by partial reduction of pyridines and Diels-Alder cycloaddition reactions using iminodienophiles.[32]

1.10.1.1.0 Reduction Reactions

The sodium borohydride reduction of pyridinium salts is still the most efficient synthetic route for synthesis of N-methyl-1,2,3,6-tetrahydropyridines.

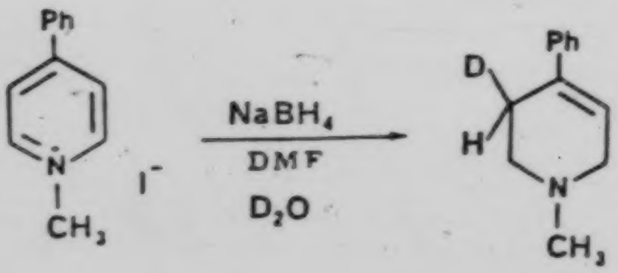


R = Me

86 87

The mechanism of the reduction of 86 to 87 was verified by deuterium labelling experiments.[96,97]

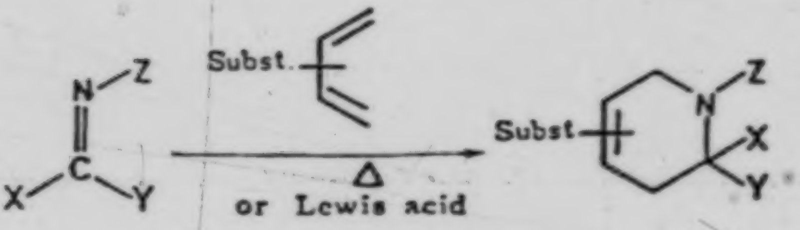
The reduction of 1-methyl-4-phenylpyridinium iodide 88 with sodium borohydride in dimethylformamide containing deuterium oxide afforded 1-methyl-3-deutero -4-phenyl-1,2,3,6-tetrahydropyridine 89. Incorporation of one deuterium atom at the C-3 position of 88 was confirmed by nuclear magnetic resonance and mass spectral analysis.[97]



88 89

1.10.1.2.0 Diels-Alder Cycloaddition Reactions Employing Tetrahydropyridines as the Dienophile

Electron deficient imines such as N-sulfonylimines and N-acylimines react with 1,3-dienes to yield 1,2,3,6-tetrahydropyridine products[98,99] (Scheme 1).



Z=SO_2Ar,Ph

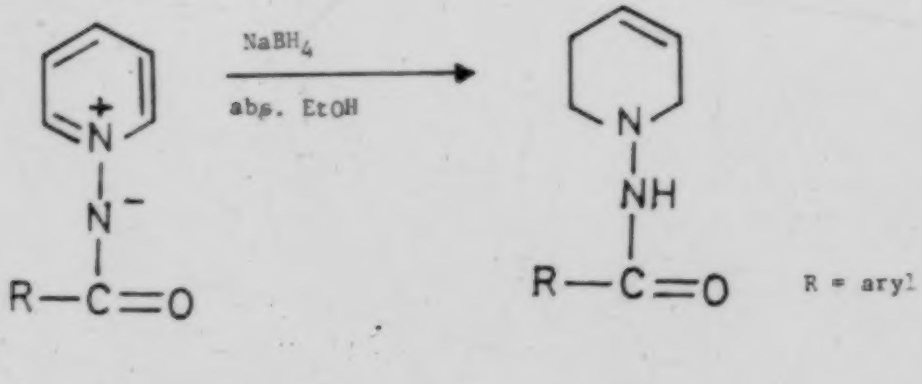
X,Y=H,CO_2CH_3,Ar,CCl_3

Scheme 1. Diels-Alder cycloaddition reactions employing imino dienophiles.

This [4+2] cycloaddition reaction can be carried out using thermal or Lewis acid catalysis reaction conditions.

1.10.1.3.0 Synthesis of 1,2,3,6-Tetrahydropyridines Using Pyridinium Ylides

1,2,3,6-Tetrahydropyridines can be prepared by the sodium borohydride reduction of N-(carbonylimino) pyridinium ylides 90 to give 91 in good yield.



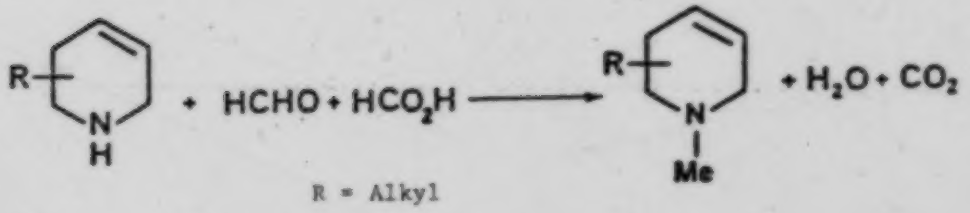
90 91

1.11.0.0.0 Chemical Properties of 1,2,3,6-Tetrahydropyridines

The reactions which 1,2,3,6-tetrahydropyridines undergo are those expected for secondary or tertiary amines and an isolated olefinic moiety. Some selected examples are described below to illustrate these reactions.

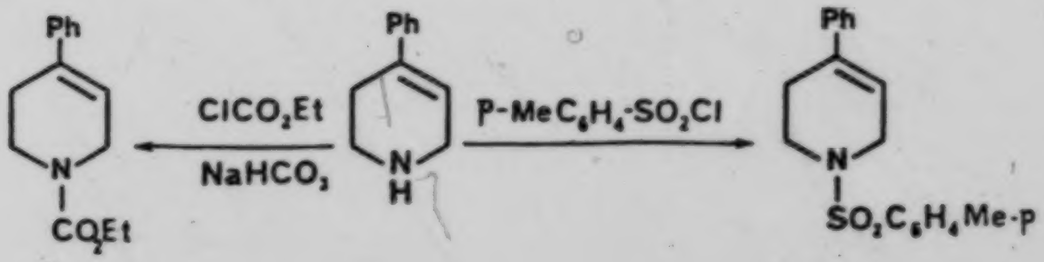
1.11.1.0.0 Reactions involving the Ring Nitrogen

Alkylation of 1,2,3,6-tetrahydropyridines 92 using the Eschweiler-Clarke reaction yielded 93.[101]


R
N
H
+ HCHO + HCO₂H
R
N
Me
+ H₂O + CO₂
R = Alkyl

92 93

Acylation of 94 with ethyl chloroformate in the presence of base gave 1-ethoxycarbonyl-4-phenyl-1,2,3,6-tetrahydropyridine 95 whereas reaction with p-toluenesulfonyl chloride yielded 1-p-toluenesulfonyl-4-phenyl-1,2,3,6-tetrahydropyridine 96.[102-104]


Ph
N
CO₂Et
ClCO₂Et
NaHCO₃
Ph
N
H
P-MeC₆H₄-SO₂Cl
Ph
N
SO₂C₆H₄Me-p

95 94 96

2.0.0.0.0 Objectives of Research

Reduction in gastric acid secretion by histamine H_2-receptor antagonists, anticholinergic drugs or by compounds that affect specific enzymes within the parietal cell continues to be the main approach to therapy for peptic ulcers. The discovery of cimetidine 9b and its clinical success have provided both the rationale and stimulus for the development of improved H_2-antagonists with improved potency, a longer duration of action and lower potential for side effects. Therefore it was of interest to determine the physicochemical properties and structural requirements for optimum H_2-receptor antagonist activity. It was also of interest to investigate:

1) The effect which replacement of the imidazole ring of cimetidine 9b by other heterocyclic ring systems such as pyridine, 1,2-dihydropyridine and 1-methyl-1,2,3,6-tetrahydropyridine had upon H_2-antagonist activity.
2) The relative activities within an isomeric series of pyridines, 1,2-dihydropyridines, and 1,2,3,6-tetrahydropyridines.
3) The importance of charge distribution in the aromatic pyridine, 1,2-dihydropyridine and 1,2,3,6-tetrahydropyridine to interactions with histamine H_2-receptors.
4) The significance of 1,2-dihydropyridine and 1,2,3,6-tetra-

hydropyridine ring systems in regard to H_2-antagonist activity.

5) The effect of replacing the terminal methyl substituent of the side chain of cimetidine 9b or ranitidine 9e by a phenyl, carbomethoxy and other alkyl or cycloalkyl substituents and replacing the terminal methylamino substituent by cycloalkylamino substituents ranging in size from five to seven membered ring systems.

6) The bioisosteric relationships between urea, thiourea cyanoguanidine and nitroethene moieties and the pyridine and 1,2-dihydropyridine ring systems.

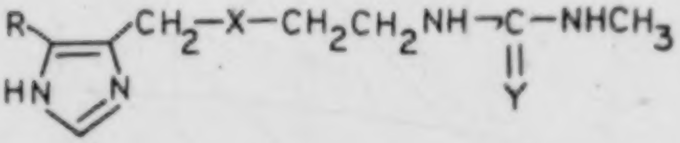
The design, synthesis and pharmacological evaluation of these different clases of structurally related compounds would provide an extensive investigation of the structure-activity relationships (SAR) for H_2-receptor antagonists.

3.0.0.0.0 DISCUSSION

3.1.0.0.0 Strategies for the Design of Novel Heterocyclic Histamine H_2-Receptor Antagonists.

The introduction of efficacious drugs for the treatment of peptic ulcer disease has stimulated interest aimed at the development of new therapeutic agents and research activity directed toward understanding the etiology of the disease. The newer therapeutic agents used for the treatment of peptic ulcer disease have been the subject of several review articles.[105-107] A book[108] and proceedings of several symposia[109,110] describing the etiology and treatment of peptic ulceration have been published recently. A collection of papers describing clinical studies involving antiulcer drugs has also been published.[111] The unprecedented success of cimetidine 9b[112] as a therapeutic agent has provided impetus for the development of second generation H_2-receptor antagonists having greater potency and specificity. A furan derivative, ranitidine (Zantac®, 9e), was ten times more potent than cimetidine *in vitro*.[113] The *in vitro* action of ranitidine was selective since high concentrations did not affect β-adrenoceptor, H_1-receptor or muscarinic receptor mediated responses.[114] The effect of ranitidine upon stimulated gastric acid secretion in normal volunteers was evaluated in several studies. Ranitidine was effective in reducing acid secretion stimulated by histamine and pentagastrin where it was six to eight times as potent as cimetidine.[115-118] No effect on prolactin secretion has been observed demonstrating that ranitidine was not a dopamine antagonist or agonist at the pituitary level.[119] Tiotidine (ICI 125211, 9d), a guanidinothiazole, was the most potent H_2-receptor antagonist reported until 1980. It exhibited at least ten times the potency of cimetidine during in vitro and in vivo studies.[120] Tiotidine has been proposed to be a useful agent for studying the effects of histamine on cardiac function and dysfunction.[121] In duodenal ulcer patients, tiotidine reduced nocturnal gastric acid secretion at doses as low as 25 mg.[122] Oxmetidine (SK&F 92994, 9f), which possesses a (3,4-methylenedioxybenzyl)pyrimidone moiety in place of the cyanoguanidine group of cimetidine, was more potent than cimetidine in vitro and was equipotent in vivo.[123] Etintidine (BL-5641, 9c), where the terminal N-methyl substituent of cimetidine was replaced by a propargyl group was intermediate in potency between cimetidine and ranitidine. It also exhibited weak anticholinergic activity.[124] Clinically, etintidine was slightly more effective than cimetidine as a inhibitor of meal-stimulated gastric acid secretion in patients with duodenal ulcers.[125] The combined H_1/H_2-histamine antagonist (SK&F 93319, 10) exhibited similar activity at both receptors giving pA_2 values of 7.77 and 7.49 respectively in the guinea pig ileum and atria assays. This compound was a more potent inhibitor of gastric secretion than cimetidine in the rat and dog when administered i.v. It was less active than mepyramine toward histamine induced bronchoconstriction in the guinea pig and acted as an antagonist at both H_1- and H_2-receptors in the peripheral vasculature.[126,127] The synthesis of 9 having a 3-bromo(hydroxy)-2-pyridyl Het substituent and a N-methylcyanoguanidine moiety Y have also been described but no H_2-antagonistic test results were reported.[128] These results make it clear that the chemical features of histamine H_2-antagonists vary with the nature of the aromatic heterocyclic ring (Het) and the moiety Y. (See structure 9). The goal of this research program was to ultimately design compounds which exhibited optimum H_2-receptors antagonistic activity using structure-activity relationship (SAR) studies. A variety of approaches were used to optimize potency based on the concept of bioisosterism which has been described in reviews by Burger,[129] Schatz,[130] Foye,[131] Korolkovas,[132] Ariens[133] and Hansch.[134]

Physicochemical properties such as acidity, hydrophilicity, dipole moment and geometry have been emphasized in developing structure-activity correlations for histamine H_2-receptor antagonists. Thiourea, urea, guanidine, cyanoguanidine and nitroguanidine comprise the variable structural moieties for a small homogeneous group of compounds (97, Y=S,O,NH,N-CN,$N\text{-}NO_2$) which provided the basis for analysis of physicochemical properties in relation to biological activity.[135,136]



97

	R	X	Y
a	H	S	NH
b	H	CH_2	S
c	Me	S	S
d	Me	S	N-CN

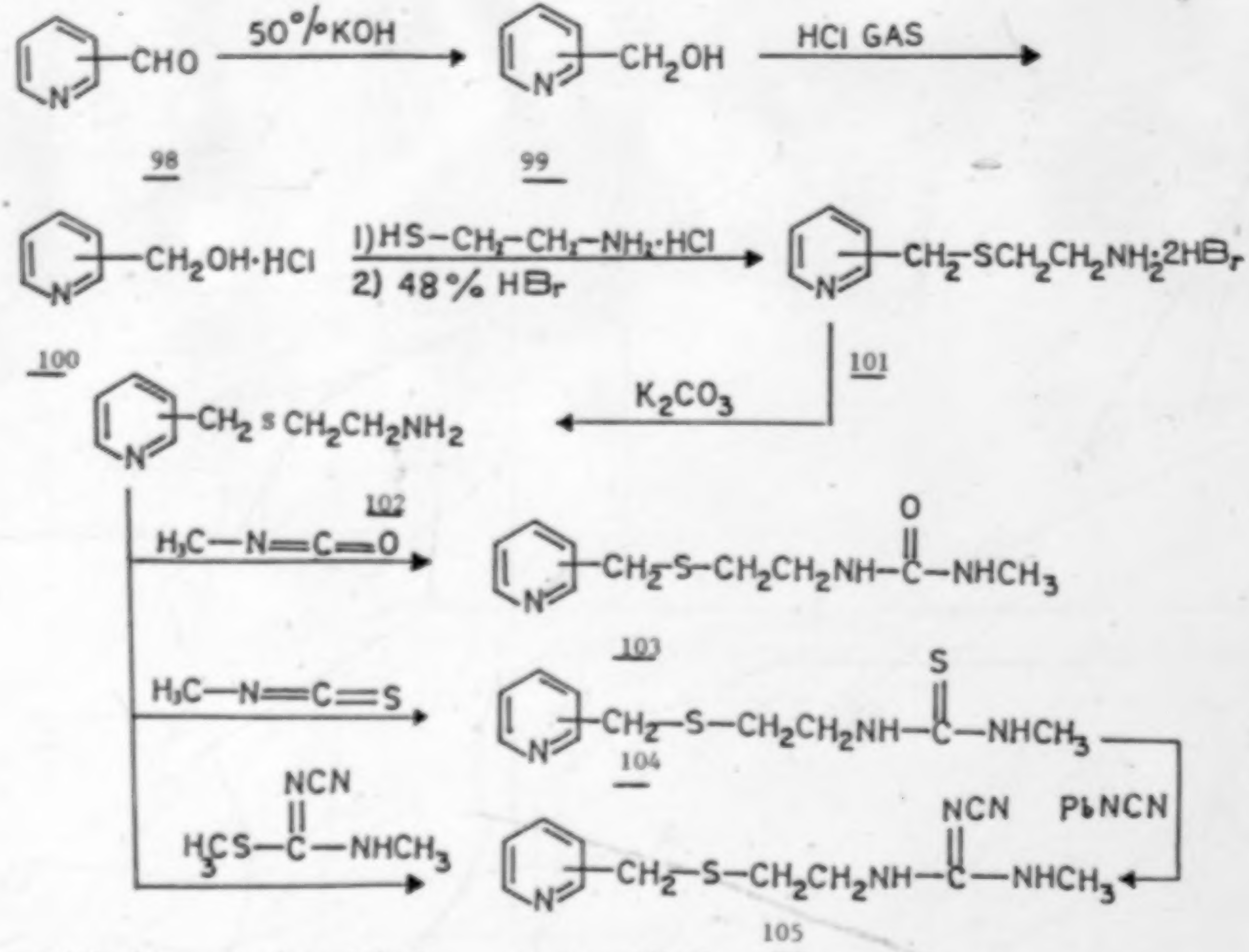
Thiourea, nitroguanidine and cyanoguanidine are therefore regarded as bioisosteres with respect to action at histamine H_2-receptors. The chemical similarity between thiourea and cyanoguanidine is illustrated by their parallel H_2-antagonist activities for various substituted imidazoles and from a detailed analysis of their physical-chemical properties.[135]

The degree of isosterism is strikingly illustrated by nearly identical molecular arrangements found in the crystal structures of metiamide[137] and cimetidine.[138] A comparison of the $-CH_2-$ and thioether (-S-) groups by X-ray crystalography and solid-state infrared spectrometry suggested that the thioether linkage may increase conformational flexibility and favor folding of the side chain. This effect may influence H_2-receptor antagonist activity.[137] An interesting correlation was found between crystal stability, melting point and aqueous solubilities of these compounds.[137] These results suggested that the $-CH_2-S-CH_2CH_2-$ moiety should be retained since it possessed the optimum distance for maximal H_2-antagonist activity when attached to a variety of Het groups. It was therefore of interest to investigate the potential utility of a pyridinyl, 1,2-dihydropyridinyl and 1-methyl-1,2,3,6-tetrahydropyridinyl ring system in place of[139,140] the 5-methyl-4-imidazolyl ring of cimetidine and the 5-dimethylaminomethyl-2-furanyl ring of ranitidine. It was also of interest to investigate the bioisosteric relationship of pyridine with 1,2-dihydropyridine. In this way one could study the effect of electron density, the point of attachment and the effect of substitution in the Het moiety upon H_2-antagonist activity. It was important to examine a number of -NH-C(=X)-NH- moieties where x was O,S,NCN and NCO_2Me to investigate their effect on H_2-antagonist activity. The effect which replacement of the terminal methyl group of the -NH-C-(=X)-NHMe moiety by other alkyl, cycloalkyl, phenyl and methoxycarbonyl substituents had on H_2-receptor antagonist activity was also worthy of investigation. These modifications were expected to influence the drug-receptor interaction.[139-141]

Clearly improved H_2-antagonists which are more selective, do not enter the central nervous system causing side effects, do not interact with β-adrenoceptor or cholinergic receptors, do not have antiandrogenic activity, do not affect cytochrome P450 and have a longer duration of action are desirable. Finally the design and synthesis of biological active compounds required an appropriate testing program. Some selected analogs were tested for H_2-receptor antagonistic activity using the chronotropic response of the guinea pig right atria to the H_2-agonist histamine dihydrochloride.

3.2.0.0.0 Synthesis of N-Methyl-N'-[2-(pyridinylmethylthio)ethyl]ureas 103, thioureas 104 and cyanoguanidines 105.

The pyridinyl urea, thiourea and cyanoguanidine analogs 103 -105 were prepared to investigate the effect of a Het pyridyl ring and its point of attachment upon H_2-antagonistic activity. The synthetic procedures used for the synthesis of the desired N-methyl-N'-[2-(pyridinylmethylthio)ethyl]ureas 103, thioureas 104 and cyanoguanidines 105 is outlined in Scheme 2 and the products obtained are summarized in Table 5. The pyridinylcarbinols 99 were prepared by the Cannizzaro


50°/°KOH
HCl GAS
98
99
1) HS–CH₂–CH₂–NH₂·HCl
2) 48% HBr
100
101
K₂CO₃
102
103
104
105
PbNCN

a, 2-pyridinyl; b, 3-pyridinyl; c, 4-pyridinyl

Scheme 2. Synthetic Routes used for the Synthesis of N-Methyl-N'-[2-(pyridinylmethylthio)ethyl] ureas 103, Thioureas 104 and Cyanoguanidines 105 .

Table 3. Some Physical Data for 2-(3-,4-)[2-Aminoethyl)thiomethyl]pyridine Dihydrobromides [101]

$R-CH_2-S-CH_2CH_2NH_2 \cdot 2HBr$

Compd	R	Yield,%	mp,°C	Formula	Calc.			Found		
					C	H	N	C	H	N
101a	2-pyridinyl	82.5	175	$C_8H_{14}N_2SBr_2$	29.09	4.24	8.48	28.76	4.28	8.43
101b	3-pyridinyl	80	182	$C_8H_{14}N_2SBr_2$	29.09	4.24	8.48	28.69	4.21	8.42
101c	4-pyridinyl	72.5	238	$C_8H_{14}N_2SBr_2$	29.09	4.24	8.48	28.85	4.19	8.75

Table 4. Infrared (ir) and Proton Magnetic Resonance (^{1}H nmr) Spectral Data for 2-(3-,4-)[(2-Aminoethyl)thiomethyl] pyridine Dihydrobromides 101

$R-CH_2-S-CH_2CH_2NH_2 \cdot 2HBr$

Compd	R	ir, cm^{-1}(KBr) (quaternary nitrogen) ir,cm^{-1},(KBr)	^{1}H nmr,δ(D$_2$O)
101a	2-pyridinyl	2600-3240	2.95(t,J=7Hz,2H,$\underline{CH}_2N$),3.35(t,J=7Hz,2H,$S\underline{CH}_2CH_2N$),4.3(s,2H,pyr^a-$\underline{CH}_2$-S-),7.9-8.3(complex m, 2H, H-3, H-5), 8.7(d,$J_{3,4}$=8Hz of d,$J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H,H-4), 8.85 (d,$J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, H-6).
101b	3-pyridinyl	2660-3260	2.9(t,J=7Hz,2H,-$\underline{CH}_2N$),3.23(t,J=7Hz,2H,$S\underline{CH}_2CH_2N$),4.03(s,2H,pyr^a-$\underline{CH}_2$-S),7.9-8.3(m,1H,pyr^{a}H-5),8.5-9.06(m,3H,pyr^{a}H-2,H-6 and H-4).

Table 4. (cont.)

101c	4-pyridinyl	2500-3300	2.93(t,J=7Hz,2H,-$\underline{CH_2}$N),3.33(t,J=7Hz,2H,S$\underline{CH_2}$CH$_2$N),4.2(s,2H,pyr[a]-$\underline{CH_2}$-S),8.21(d,$J_{2,3}=J_{5,6}$=6Hz,2H,pyr[a]H-3,H-5), 8.83 (d,$J_{2,3}=J_{5,6}$=6Hz,2H,pyr[a]H-2,H-6).

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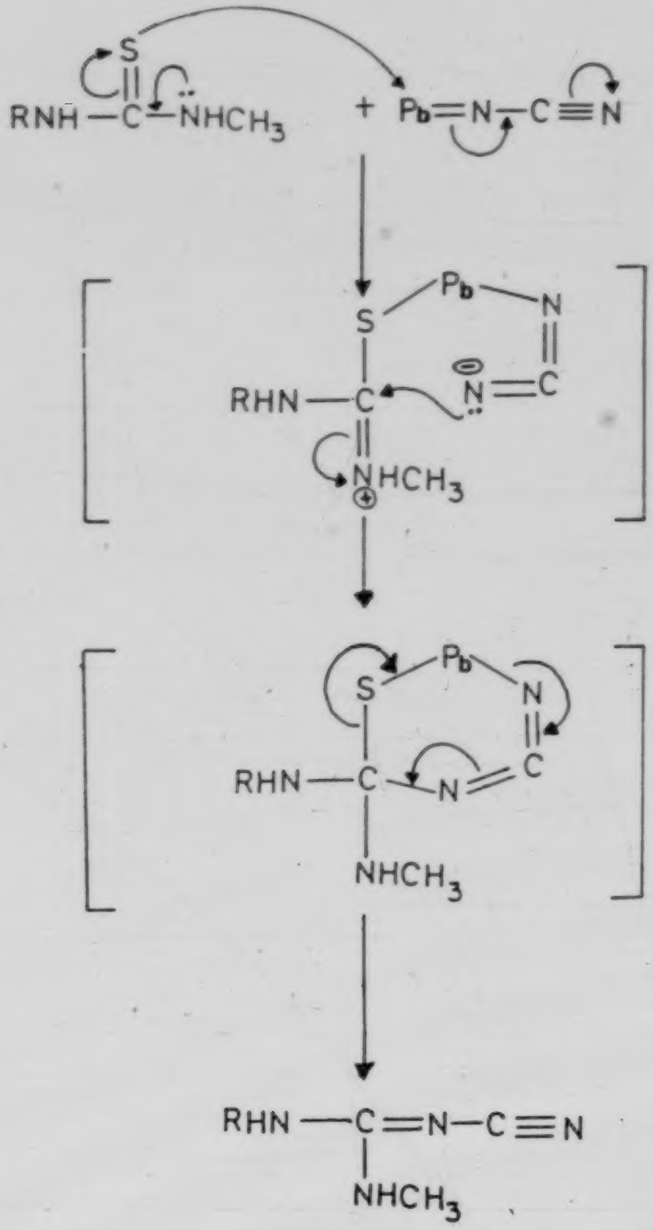
[a] pyr denotes pyridine

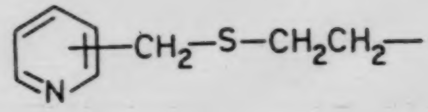
reaction[142] starting with the corresponding pyridinylcarboxaldehydes 98. Reaction of the pyridinylcarbinol hydrochlorides 100 with cysteamine hydrochloride followed by treatment with 48% hydrobromic acid afforded the 2-aminoethylthiomethylpyridine dihydrobromides 101 in good yield (See Table 3).

The structure assigned to 101a was consistent with the ir, ^{1}H nmr and microanalytical data obtained. The ir spectrum revealed the presence of a quaternary nitrogen in the 2600-3240 cm^{-1} range. The ^{1}H nmr spectrum in deuterium oxide (δ) exhibited a 2H triplet (J=7Hz) at 2.95 assigned to the $-\underline{CH}_2N$, a 2H triplet (J=7Hz) at 3.35 due to the $S\underline{CH}_2CH_2N$, a 2H singlet at 4.3 due to the 2-pyridinyl-$\underline{CH}_2$-S, a complex 2H multiplet at 7.9-8.3 attributed to the pyridinyl H-3 and H-5 protons, a 1H doublet ($J_{3,4}$=8Hz) of doublet ($J_{4,5}$=8Hz) of doublet ($J_{4,6}$=2Hz) at 8.7 attributed to the pyridinyl H-4 and a 1H doublet ($J_{5,6}$=5Hz) of doublet ($J_{4,6}$=2Hz) at 8.85 due to the pyridinyl H-6.

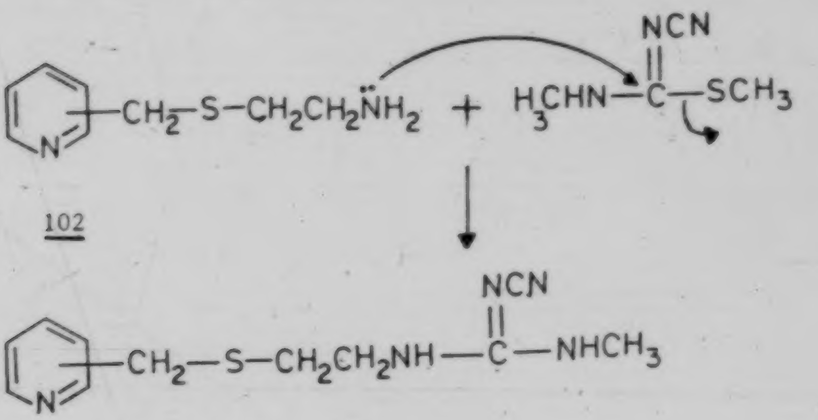
The subequent reaction of 102 with methylisocyanate, methylisothiocyanate or S-methyl-N-cyano-N'-methylcarbamimidothioate gave the respective urea 103, thiourea 104 and cyanoguanidine 105 derivatives. Alternatively, the cyanoguanidines 105 were also prepared by reaction of 104 with lead cyanamide.[143] The ir and ^{1}H nmr spectral data for compounds 103-105 are summarized in Table 6. The reaction of the thiourea derivative 104 with lead cyanamide in acetonitrile-dimethylformamide at reflux afforded the cyanoguanidine analogs 105 as illustrated below.


RNH
S
NHCH$_3$
+
Pb=N−C≡N
Pb
N
C
RHN
NHCH$_3$
RHN−C=N−C≡N
NHCH$_3$

R =


N
CH$_2$−S−CH$_2$CH$_2$−

Alternatively, the cyanoguanidine derivatives 105 can be prepared by reaction of the amine 102 with S-methyl-N-cyano-N'- methylcarbamimidothioate as illustrated below.

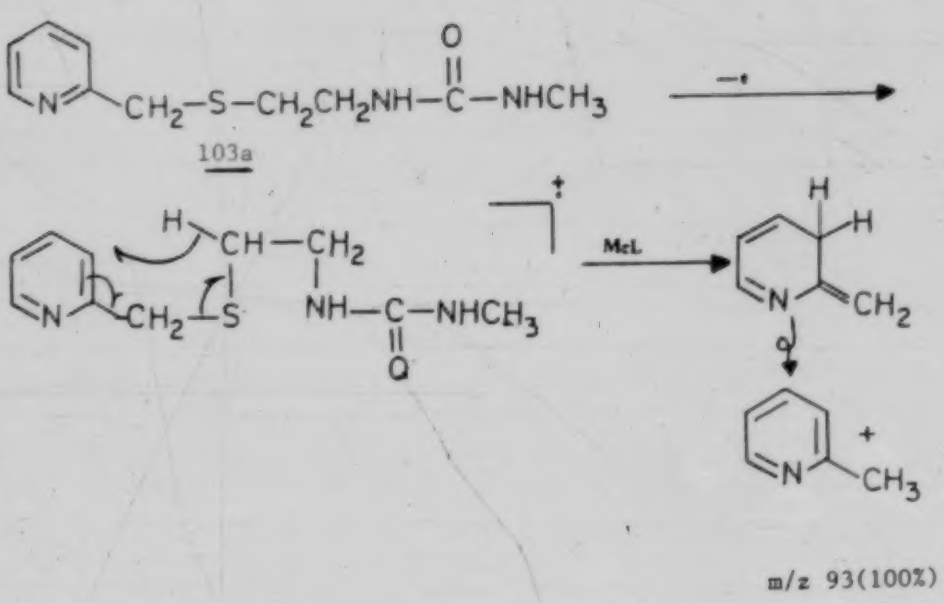


102

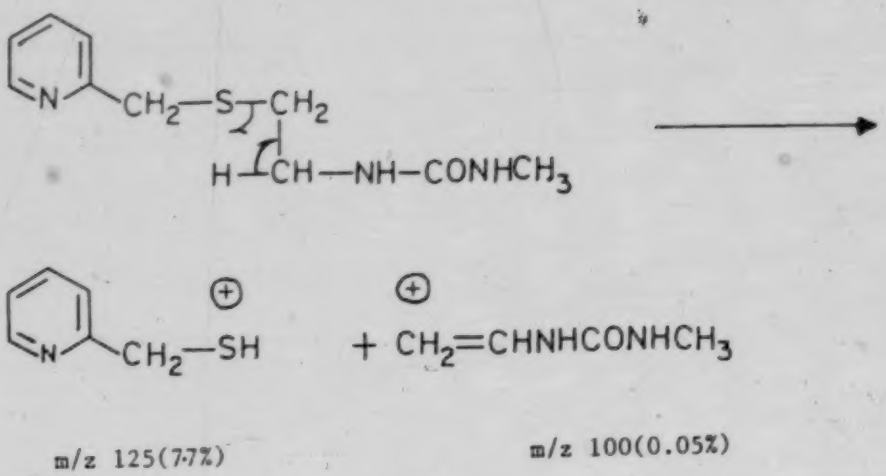
105

The structure assigned to 103a was consistent with the ir, ^{1}H nmr and mass spectral data obtained. The ir spectrum revealed the presence of a NH at 3350 and a CO group at 1650cm^{-1}. The ^{1}H nmr spectrum in deuterochloroform (δ) exhibited a 2H triplet (J=7Hz) at 2.78 assigned to -$\underline{CH_2}$-N, a 3H doublet ($J_{NH,Me}$=5Hz) at 3.08, which collapsed to a singlet upon deuterium oxide exchange, attributed to the NH$\underline{CH_3}$, a 2H triplet (J=7Hz) at 3.85 due to the -SCH$_2$CH$_2$N, a 2H singlet at 3.9 assigned to the pyridinyl-$\underline{CH_2}$-S-, a 4H multiplet at 6.6-7.55 assigned to the pyridinyl H-3 and H-5 and two NH protons, which exchanged with deuterium oxide, a 1H doublet ($J_{3,4}$=8Hz) of doublet ($J_{4,5}$=8Hz) of doublet ($J_{4,6}$=2Hz) at 7.78 assigned to the pyridinyl H-4 and a 1H doublet ($J_{5,6}$=5Hz) of doublet ($J_{4,6}$=2Hz) at 8.57 due to the pyridinyl H-6. The mass spectrum exhibited a molecular ion at m/z 225.0934 (2.47%). The major fragmention pathways for 103a are shown in Scheme 3.

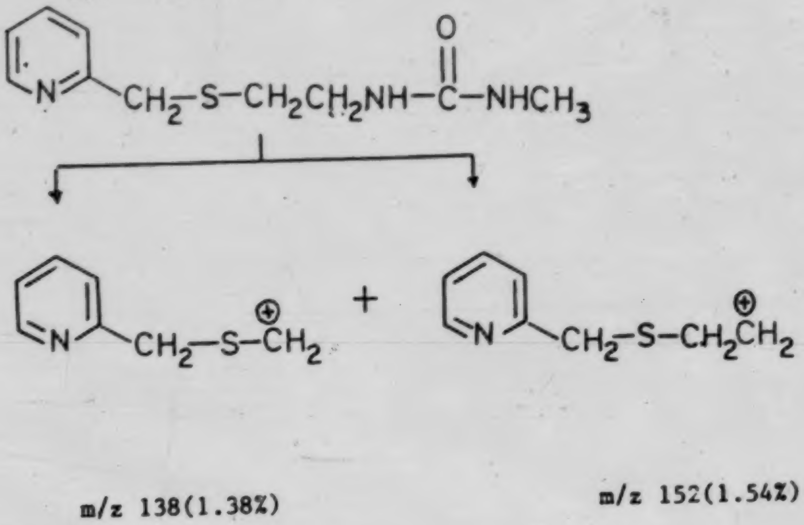
A)


103a
McL
m/z 93(100%)

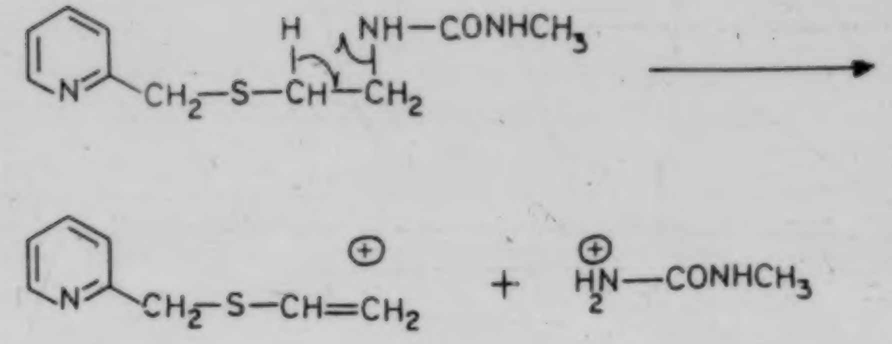
B)


m/z 125(7.7%)
m/z 100(0.05%)

C)


m/z 138(1.38%)
m/z 152(1.54%)

D)



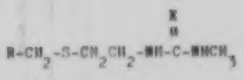
m/z 151(1.64%)

m/z 74(1.27%)

Scheme 3. Major Fragmentation Pathways for N-Methyl-N'-[(2-pyridinylmethylthio)ethyl]urea 103a.

The base peak at m/z 93(100%) could be formed by direct cleavage of the C-S bond adjacent to the 2-pyridyl ring accompanied by hydrogen transfer from CH_2SCH_2 to the pyridine ring as illustrated by Path A Scheme 3 to give a 2-picolinium ion. On the other hand if cleavage of the C-S bond of the $S\text{-}CH_2CH_2NH$ moiety occurred and was accompanied by hydrogen transfer from CH_2NH to the sulfur atom the 2-pyridylcarbinthiol at m/z 125 (7.7%) ion would be produced as shown by Path B Scheme 3. Fragmentation of the C-C and C-N bonds as illustrated by Path C Scheme 3 would result in the formation of a 2-pyridinylmethylthiomethyl ion at m/z 138(1.38%) and a 2-pyridinylmethylthioethyl ion at m/z 152(1.54%). Alternatively, cleavage of the CH_2-NH bond with hydrogen transfer from SCH_2 to CH_2NH as depicted for Path D Scheme 3 could give rise to the 2-pyridinylmethylthioethenium ion at m/z 151 (1.27%) and an ion at m/z 74 (1.64%) due to N-methylurea.

Table 5. Some Physical Data for N-Methyl-N'-[2-(2-(3-,4-)pyridinylmethylthioethyl]ureas 103, thioureas 104 and cyanoguanidines 105.



$$R\text{-}CH_2\text{-}S\text{-}CH_2CH_2\text{-}NH\text{-}\overset{\overset{X}{\|}}{C}\text{-}NHCH_3$$

Compd	R	X	Yield, %	mp, °C	Formula	Exact Mass		Calcd.			Found		
						Calcd	Found	C	H	N	C	H	N
103a	2-pyridinyl	O	82	oil	$C_{10}H_{15}N_3OS$	225.0935	225.0934		———			———	
103b	3-pyridinyl	O	80	oil	$C_{10}H_{15}N_3OS$	225.0935	225.0937		———			———	
103c	4-pyridinyl	O	81	oil	$C_{10}H_{15}N_3OS$	225.0935	225.0936		———			———	
104a	2-pyridinyl	S	65	155	$C_{10}H_{15}N_3S_2$[a]	241.0707	241.0704	40.85	3.82	17.87	40.80	3.84	17.64
104b	3-pyridinyl	S	62	165	$C_{10}H_{15}N_3S_2$[a]	241.0707	241.0707	40.85	3.82	17.87	40.78	3.83	17.39
104c	4-pyridinyl	S	70	135	$C_{10}H_{15}N_3S_2$[a]	241.0708	241.0705	40.85	3.82	17.87	40.92	3.85	17.43
105a	2-pyridinyl	NCN	70	112	$C_{11}H_{15}N_5S$	———	———	52.99	6.05	28.08	52.46	6.11	27.67
105b	3-pyridinyl	NCN	72	140	$C_{11}H_{15}N_5S$	———	———	52.99	6.05	28.08	52.78	6.16	27.72
105c	4-pyridinyl	NCN	80	165	$C_{11}H_{15}N_5S$	249.1048	249.1051	52.99	6.05	28.08	52.72	6.21	27.52

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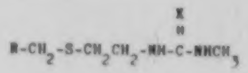
[a] Picrate salt

Table 6. Infrared (ir) and Proton Magnetic Resonance (^{1}H nmr) Spectral Data for N-Methyl-N'-[(2-(3-,4-)pyridinylmethylthio]ethyl]ureas 103, thioureas 104 and cyanoguanidines 105.



$$R\text{-}CH_2\text{-}S\text{-}CH_2CH_2\text{-}NH\text{-}\overset{X}{\overset{\|}{C}}\text{-}NHCH_3$$

Compd	R	X	ir, cm^{-1} (KBr) C=X	ir, cm^{-1} (KBr) NH	^{1}H nmr, δ (CDCl$_3$)
103a	2-pyridinyl	O	1650	3350	2.78 (t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.08 (d, $J_{NH,Me}$=5Hz, 3H, NH$\underline{CH_3}$, collapses to a singlet after deuterium oxide exchange), 3.85 (t, J=7Hz, 2H, -S-$\underline{CH_2}$CH$_2$), 3.9 (s, 2H, pyr^a-$\underline{CH_2}$-S), 6.6-7.59 (m, 4H, H-3, H-5, two NH protons, exchange with deuterium oxide), 7.78 (d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, H-4), 8.57 (d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, H-6).
103b	3-pyridinyl	O	1650	3360	2.61 (t, J=7Hz, 2H, -$\underline{CH_2}$N), 2.9 (d, $J_{NH,Me}$=5Hz, 3H, NH$\underline{CH_3}$, collapses to a singlet after deuterium oxide exchange) - 3.73 (t, J=7Hz, 2H, -S$\underline{CH_2}$CH$_2$-), 3.7 (s, 2H, pyr^a-$\underline{CH_2}$-S), 6.5-7.46 (m, 3H, pyr^a H-5, two NH protons, exchange with

Table 6. (cont.)

					deuterium oxide), 7.5-7.86(m, 1H, pyr^{a} H-4), 8.2-8.66 (m, 2H, pyr^{a} H-2, ,H-6).
101c	4-pyridinyl	O	1650	3360	2.56(t, J=7Hz, 2H, -$\underline{CH_2}$N), 2.8(d, $J_{NH,Me}$=5Hz, 3H, NH$\underline{CH_3}$, collapses to a singlet after deuterium oxide exchange), 3.48(t, J=7Hz, 2H S$\underline{CH_2}$CH$_2$), 3.74 (s, 2H, pyr^{a}-$\underline{CH_2}$-S), 5.43-6.33 (br m, 2H, 2NH protons, exchange with deuterium oxide), 7.31 (d, $J_{2,3}$=$J_{5,6}$=6Hz, 2H, pyr^{a} H-3,H-5), 8.56(d, $J_{2,3}$=$J_{5,6}$=6Hz, 2H, pyr^{a} H-2, H-6).
104a	2-pyridinyl	S	1090	3280	2.78(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.08 (d, $J_{NH,Me}$=5Hz, 3H, NH$\underline{CH_3}$, collapses to a singlet after deuterium oxide exchange), 3.76(t, J=7Hz, 2H, S$\underline{CH_2}$CH$_2$), 3.9(s, 2H, pyr^{a}-$\underline{CH_2}$-S), 6.82-7.52(m, 4H, H-3, H-5, two NH protons, exchange with deuterium oxide), 7.76 (d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, H-4), 8.6(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, H-6).
104b	3-pyridinyl	S	1090	3290	2.75(t, J=7Hz, 2H,-$\underline{CH_2}$N), 3.06(d, $J_{NH,Me}$=5Hz, 3H, -NHCH$_3$, collapses to a singlet after deuterium oxide

Table 6. (cont.)

					exchange), 3.74(t, J=7Hz, 2H, SCH_2CH_2), 3.81 (s, 2H, pyr*-CH_2-S), 6.50-7.2(m, 2H, two NH protons, exchange with deuterium oxide), 7.2-7.53(m, 1H, pyr* H-5), 7.66-7.96(m, 1H, pyr* H-4); 8.43-8.74(m, 2H, pyr* H-2, H-6).
104c	4-pyridinyl	S	1090	3290	2.73(t, J=7Hz, 2H, -CH_2N), 3.05(d, $J_{NH,Me}$=5Hz, 3H, NHCH_3, collapses to a singlet after deuterium oxide exchange), 3.76(t, J=7Hz, 2H, SCH_2CH_2N), 3.78 (s, 2H, pyr* -CH_2S), 6.5-7.16 (m, 2H, two NH protons, exchange with deuterium oxide), 7.38 (d, $J_{2,3}$=$J_{5,6}$=6Hz, 2H, pyr* H-3, H-5), 8.59(d $J_{2,3}$=$J_{5,6}$=6Hz, 2H, pyr* H-2, H-6).
105a	2-pyridinyl	NCN	2170	3330	2.74(t, J=7Hz, 2H, -CH_2N), 3.05(d, $J_{NH,Me}$=5Hz, 3H, NHCH_3, collapses to a singlet after deuterium oxide exchange), 3.7(t, J=7Hz, 2H, SCH_2CH_2N), 3.86(s, 2H, pyr*-CH_2-S), 6.72-7.5(m, 4H, H-3, H-5, two NH protons which exchange with deuterium oxide), 7.7(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, H-4), 8.52(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, H-6).

Table 6. (cont.)

105b	3-pyridinyl[b]	NCN	2180	3310	2.56(t, J=7Hz, 2H, -$\underline{\mathrm{CH}}_2$N), 2.74(d, $_{\mathrm{NH,Me}}$=5Hz, 3H, NH$\underline{\mathrm{CH}}_3$, collapses to a singlet after deuterium oxide exchange), 3.33(t, J=7Hz, 2H, S$\underline{\mathrm{CH}}_2CH_2$), 3.86 (s, 2H, pyr[a]-$\underline{\mathrm{CH}}_2$-S), 6.86-7.2(m, 2H, two NH protons which exchange with deuterium oxide), 7.2-7.63(m, 1H, pyr[a] H-5), 7.63-7.96(m, 1H, pyr[a] H-4), 8.33-8.73(m, 2H, pyr[a] H-2, H-6).
105c	4-pyridinyl[c]	NCN	2180	3310	2.56(t, J=7Hz, 2H, -$\underline{\mathrm{CH}}_2$N), 2.68(d, $J_{\mathrm{NH,Me}}$=5Hz, 3H, NH$\underline{\mathrm{CH}}_3$, collapses to a singlet after deuterium oxide exchange), 3.33(t, J=7Hz, 2H, S$\underline{\mathrm{CH}}_2CH_2$N), 3.85(s, 2H, pyr[a]-$\underline{\mathrm{CH}}_2$-S), 6.8-7.23(m, 2H, two NH protons, exchange with deuterium oxide), 7.44(d, $J_{2,3}$=$J_{5,6}$=6Hz, 2H, pyr[a] H-3, H-5), 8.63(d, $J_{2,3}$=$J_{5,6}$=6Hz, 2H, pyr[a] H-2, H-6).

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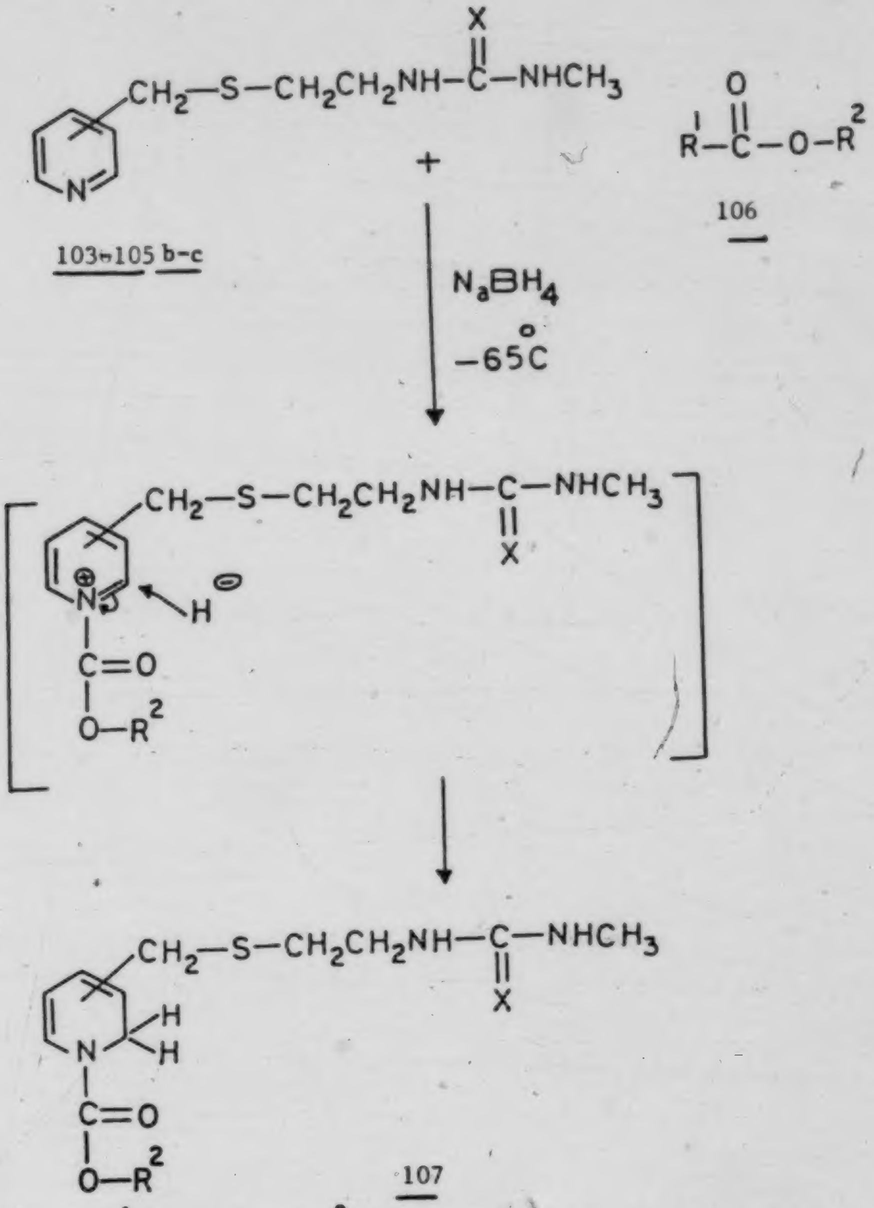
[a] pyr denotes pyridine

[b] The spectrum was determined in DMSO-d_6.

[c] The spectrum was determined in a mixture of CDCl$_3$ and DMSO-d_6.

3.3.0.0.0 Synthesis of N-Methyl-N'-{2-[3-(4-) (1-alkyl(aryl)-oxycarbonyl-1,2-dihydropyridinylmethylthio]ethyl}ureas, thioureas and cyanoguanidines 107.

A series of 1-alkyl(aryl)oxycarbonyl-1,2-dihydropyridinyl analogs 107 were prepared to investigate the effect which reduction of the pyridinyl ring of 103-105 b-c to a 1,2-dihydropyridinyl ring analog 107 had upon H_2-antagonist activity. This study would also provide information regarding the importance of the position of attachment of the side chain to the 1,2-dihydropyridinyl ring and the effect of various 1-alkyl or aryl substituents with respect to H_2-antagonist activity. In this way it may be possible to obtain data which would confirm or dispute the possibility that an appropriately substituted pyridinyl ring is bioisosteric to a 1,2-dihydropyridinyl ring with respect to histamine H_2-receptor antagonist activity. The sodium borohydride reduction of the pyridine derivatives 103-105 b-c in the presence of methyl chloroformate, phenyl chloroformate or di-tert-butylcarbonate in methanol at -65°C yielded the respective 1,2-dihydropyridinyl analogs 107 in good yield as illustrated by Scheme 4 and summarized in Table 7.[144, 145]

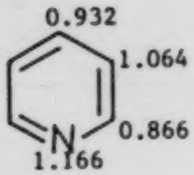

103-105 b-c
106
NaBH4
-65°C
107

X=O,S,NCN; R^1=Cl,O-tBu, R^2=CH_3,Ph,O-t-Bu

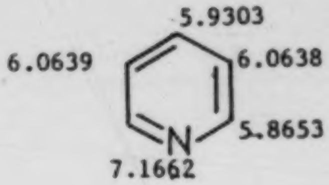
Scheme 4. Synthetic Routes used for the Synthesis of N-Methyl-N'-{2-[3-(4-)(1-alkyl(aryl)oxycarbonyl-1.2-dihydropyridinylmethylthio]ethyl}ureas, thioureas and cyanoguanidines. 107

Attack by borohydride anion appears to be regiospecific and to take place only at the C-2 position of the intermediate 3-substituted pyridinium salts to afford 3-substituted-1,2-dihydropyridinyl analogs 107. This regiospecificity is likely due to the $-CH_2$-S- moiety of the side chain which could complex to borohydride thereby directing attack at the C-2 position. It is unlikely that the negative inductive effect exerted by the $-CH_2S-$ moiety would cause a sufficient reduction in the electron density at C-2 relative to C-6 to influence the site of attack. The structure assigned to 112 is consistent with its ir, ^{1}H nmr, mass spectrum and microanalytical results. The ir spectrum showed an NH absorption at 3320, a CN absorption at 2180 and a CO absorption at 1710 cm^{-1}. The ^{1}H nmr spectrum (δ)of 112 ($CDCl_3$) exhibited a 2H triplet (J=7Hz) at 2.7 assigned to $-\underline{CH_2}N$, a 3H doublet (J=5Hz) at 3.02 assigned to $NH\underline{CH_3}$ which collapsed to a singlet upon deuterium oxide exchange, a 2H singlet at 3.25 due to the 1,2-dihydropyridinyl-$\underline{CH_2}$-S, a 2H triplet (J=7Hz) at 3.75 attributed to $S\underline{CH_2}CH_2$, a 3H singlet at 3.82 for the $O\underline{CH_3}$, a broad 2H singlet at 4.4 assigned to the 1,2-dihydropyridinyl H-2, a 1H doublet ($J_{4,5}$=6Hz) of doublet ($J_{5,6}$=8Hz) at 5.2 attributed to the 1,2-dihydropyridinyl H-5, a 1H doublet ($J_{4,5}$=6Hz) at 5.85 assigned to the 1,2-dihydropyridinyl H-4, a broad 2H multiplet at 6.5 assigned to the two NH protons, which exchange with deuterium oxide and a 1H doublet ($J_{5,6}$=8Hz) at 6.73 assigned to 1,2-dihydropyridinyl H-6.

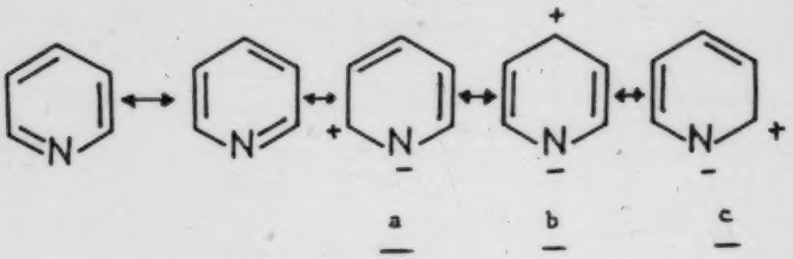
It is known that substitution of -CH in benzene by -N-(pyridine) alters the ground state electron distribution significantly. Since nitrogen is more electronegative than carbon, it tends to decrease the π-electron density at the C-2 and C-6 carbon atoms in the ring system.



Ground state π-electron densities for pyridine



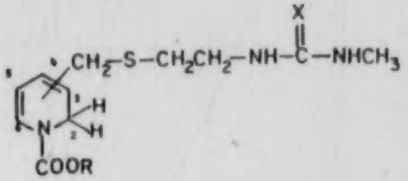
Atomic electron populations for pyridine



Resonance structures for pyridine

The carbon atoms that are α and γ to the nitrogen atom in pyridine have a ground state π-electron density of less than one. Molecular orbital calculations of the atomic electron population for pyridine provided similar results. Application of the concepts of resonance theory provide further information regarding the electron densities at the various positions for pyridine. The α-position should be more positive than the γ-position since two resonance contributing structures can be drawn for the α-carbons (a, c) whereas only one resonance contributing structure can be written for the γ-carbon b.[146]

Table 7. Some Physical Data for N-Methyl-N'-[2-[(3-(4-)-1-alkyl(aryl)oxycarbonyl-1,2-dihydropyridinylmethylthio]ethyl] ureas, thioureas and cyanoguanidines 107



Compd.	Attachment	R	X	Reaction Time(h)	Rf	Yield,%	mp,°C[a]	Formula[b]	Exact Mass Calcd	Exact Mass Found	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
108	C-3	CH_3	O	3	0.6	71	137	$C_{12}H_{19}N_3O_3S$	285.1147	285.1150	20.73	3.02	6.04	21.17	2.58	6.16
109	C-4	CH_3	O	3	0.52	70	141	$C_{12}H_{19}N_3O_3S$	285.1147	285.1135	20.73	3.02	6.04	21.06	2.50	6.24
110	C-3	CH_3	S	3	0.73	54	129	$C_{12}H_{19}N_3O_2S_2$	301.0918	301.0915	20.3	2.95	5.90	21.10	2.54	6.18

Table _7_. (cont.)

_111_	C-4	CH_3	S	3	0.7	55	136	$C_{12}H_{19}N_3O_2S_2$	301.0918	301.0917	20.3	2.95	5.90	21.08	2.50	6.35
_112_	C-3	CH_3	NCN	3	0.69	56	118	$C_{13}H_{19}N_5O_2S$	309.1260	309.1249	21.70	2.92	9.73	21.22	2.53	9.24
_113_	C-4	CH_3	NCN	3	0.71	50	127	$C_{13}H_{19}N_5O_2S$	309.1260	309.1261	21.70	2.92	9.73	21.48	2.56	9.22
_114_	C-3	C_6H_5	O	3	0.73	70	150	$C_{17}H_{21}N_3O_3S$	347.1304	347.1301	26.96	3.03	5.54	26.75	3.21	6.01
_115_	C-4	C_6H_5	O	3	0.7	70	163	$C_{17}H_{21}N_3O_3S$	347.1304	347.1304	26.96	3.03	5.54	27.18	2.30	6.16
_116_	C-3	C_6H_5	S	3	0.69	70	145	$C_{17}H_{21}N_3O_2S_2$	363.1075	363.1045	26.40	2.97	5.43	26.14	3.10	5.97
_117_	C-4	C_6H_5	S	3	0.65	73	152	$C_{17}H_{21}N_3O_2S_2$	363.1075	363.1045	26.40	2.97	5.43	26.01	3.03	6.40

Table 7. (cont.)

118	C-3	C_6H_5	NCN	2.5	0.77	70	139	$C_{18}H_{21}N_5O_2S$	371.1429	371.1421	27.67	2.94	8.96	26.95	2.31	9.28
119	C-4	C_6H_5	NCN	3	0.6	72	147	$C_{18}H_{21}N_5O_2S$	--------	--------	27.67	2.94	8.96	27.02	2.31	9.27
120	C-3	t-C_4H_9	O	5	0.79	67	112	$C_{15}H_{25}N_3O_3S$	327.1616	327.1617	24.43	3.66	5.69	24.71	3.25	6.23
121	C-4	t-C_4H_9	O	5	0.75	67	125	$C_{15}H_{25}N_3O_3S$	--------	--------	24.43	3.66	5.69	24.52	3.34	6.00
122	C-3	t-C_4H_9	S	5	0.8	70	128	$C_{15}H_{25}N_3O_2S_2$	343.1389	343.1376	23.91	3.58	5.57	23.63	3.10	6.17
123	C-4	t-C_4H_9	S	5	0.8	72	133	$C_{15}H_{25}N_3O_2S_2$	343.1389	343.1394	23.91	3.58	5.57	23.83	3.11	5.94
124	C-3	t-C_4H_9	NCN	5	0.76	73	117	$C_{16}H_{25}N_5O_2S$	--------	--------	25.24	3.54	9.19	25.51	3.30	9.43

Table 7. (cont.)

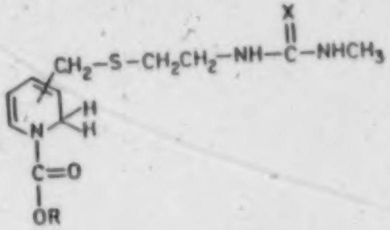
125	C-4	t-C_4H_9	NCH	5	0.9	72	126	$C_{16}H_{25}N_5O_2S$	--------	--------	25.24	3.54	9.19	25.52	3.31	9.25

---

[a] The dihydrogen hexachloroplatinate salts were prepared since other salts as the HCl, HBr, oxalate and picrate salts did not provide good crystalline products for micro elemental analysis. These derivatives were either sticky masses or very hygroscopic salts. However the dihydrogen hexachloroplatinate salts may contain one or two molecules of dihydrogen hexachloroplatinate or consist of a mixture of the two.

[b] All compounds were analyzed as their dihydrogen hexachloroplatinate salts for C, H, and N and/or for C, H, N, O and S using high resolution mass spectrometry.

Table 8. Infrared (ir) and Proton Magnetic Resonance (^{1}H nmr) Spectral Data for N-Methyl-N'-{2-[3-(4-)1-alkyl(aryl)oxycarbonyl-1,2-dihydropyridinylmethylthio]ethyl}ureas, thioureas and cyanoguanidines [107]



Compd	Point of Attachment	R	X	ir, cm^{-1} (KBr) C=N	C=O	NH	^{1}H nmr, δ(CDCl$_3$)
108	C-3	CH$_3$	O	1624	1704	3320	2.7(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.02(d, J=5Hz, 3H, N-$\underline{CH_3}$, collapses to a singlet on deuterium oxide exchange), 3.25(s, 2H, dihydropyridinyl-$\underline{CH_2}$-S), 3.75(t, J=7Hz, 2H, S$\underline{CH_2}$CH$_2$N), 3.82(s, 3H, O$\underline{CH_3}$).

Table 8. (cont.)

							4.4(br s, 2H, dihydropyridinyl H-2), 5.2(d, $J_{4,5}$=6Hz of d, $J_{5,6}$=8Hz, 1H, H-5), 5.85(d, $J_{4,5}$=6Hz, 1H, H-4), 6.5(br m, 2H, two NH protons, exchange with deuterium oxide), 6.73(d, $J_{5,6}$=8Hz, 1H, H-6).
109	C-4	CH_3	O	1624	1704	3320	2.96(t, J=7Hz, 2H, $-\underline{CH}_2N$), 3.26(d, J=5Hz, 3H, $N-\underline{CH}_3$, collapses to a singlet after deuterium oxide exchange), 3.4(s, 2H, dihydropyridinyl-$\underline{CH}_2$-S), 3.93(t, J=7Hz, 2H, $S\underline{CH}_2CH_2N$), 4.1(s, 3H, $O\underline{CH}_3$), 4.63(d, J=4Hz, dihydropyridinyl H-2), 5.23-5.83(m, 2H, H-3, H-5), 6.33-6.93(m, 2H, two NH protons, exchange with deuterium oxide), 7.03(d, $J_{5,6}$=8Hz, 1H, H-6).
110	C-3	CH_3	S	1090	1704	3320	2.63(t, J=7Hz, 2H, $-\underline{CH}_2N$), 2.9(d, J=5Hz, 3H, $N-\underline{CH}_3$, collapses to a singlet on deuterium oxide exchange), 3.13(s, 2H, dihydropyridinyl-$\underline{CH}_2$-S), 3.7(t, J=7Hz, 2H, $S\underline{CH}_2CH_2N$), 3.8(s, 3H, $O\underline{CH}_3$), 4.3

Table __8__. (cont.)

							(br m, 2H, dihydropyridinyl H-2), 5.13(d, $J_{4,5}$=6Hz of d, $J_{5,6}$=8Hz, 1H, H-5), 5.75(d, $J_{4,5}$=6Hz, 1H, H-4), 6.2(br m, 2H, two NH protons, exchange with deuterium oxide), 6.7(d, $J_{5,6}$=8Hz, 1H, H-6).
__111__	C-4	CH$_3$	S	1090	1710	3300	2.71(t, J=7Hz, 2H, -$\underline{\text{CH}_2}$N), 3.02(d, J=5Hz, 3H, N$\underline{\text{CH}_3}$, collapses to a singlet on deuterium oxide exchange), 3.08(m, 2H, dihydropyridinyl-$\underline{\text{CH}_2}$-S), 3.73(t, J=7Hz, 2H, S$\underline{\text{CH}_2}$CH$_2$N), 3.8(s, 3H, O$\underline{\text{CH}_3}$) 4.4(d, J=4Hz, 2H, dihydropyridinyl H-2), 5.2-5.63 (m, 2H, H-3, H-5), 6.1-6.63 (m, 2H, two NH protons, exchange with deuterium oxide), 6.98(d, $J_{5,6}$=8Hz, 1H, H-6).
__112__	C-3	CH$_3$	NCN	2180	1710	3320	2.7(t, J=7Hz, 2H, -$\underline{\text{CH}_2}$N), 3.02(d, J=5Hz, 3H, N-$\underline{\text{CH}_3}$, collapses to a singlet after deuterium oxide exchange), 3.25(m, 2H, dihydropyridinyl-$\underline{\text{CH}_2}$-S), 3.75(t, J=7Hz, 2H, S$\underline{\text{CH}_2}$CH$_2$N), 3.82(s, 3H, O$\underline{\text{CH}_3}$), 4.4(br s, 2H, dihydropyridinyl H-2), 5.2(d,

Table 8. (cont.)

							$J_{4,5}$=6Hz of d, $J_{5,6}$=8Hz, 1H, H-5), 5.05 (d, $J_{4,5}$=6Hz, 1H, H-4), 6.5(br m, 2H, two NH protons, exchange with deuterium oxide), 6.73 (d, $J_{5,6}$=8Hz, 1H, H-6).
113	C-4	CH_3	NCN	2180	1710	3320	2.7(t, J=7Hz, 2H, $-\underline{CH_2}N$), 2.96(d, J=5Hz, 3H, $N-CH_3$, collapses to a singlet on deuterium oxide exchange), 3.1(m, 2H, dihydropyridinyl-$\underline{CH_2}$-S), 3.66(t, J=7Hz, 2H, $S\underline{CH_2}CH_2N$), 3.75(s, 3H, $O\underline{CH_3}$), 4.3(d, J=3Hz, 2H, dihydropyridinyl H-2), 4.95-5.5 (m, 2H, H-3, H-5), 6.35(m, 2H, two NH protons, exchange with deuterium oxide), 6.75(d, $J_{5,6}$=8Hz, 1H, H-6).
114	C-3	C_6H_5	O	1624	1704	3320	2.65(t, J=7Hz, 2H, $-\underline{CH_2}N$), 2.85(d, J=5Hz, 3H, $N\underline{CH_3}$, collapses to a singlet after deuterium oxide exchange), 3.2(m, 2H, dihydropyridinyl $-\underline{CH_2}$-S), 3.73(t, J=7Hz, $S\underline{CH_2}CH_2N$), 4.53(distorted d, J=3Hz, 2H, dihydropyridinyl H-2), 5.35(d, $J_{4,5}$=6Hz of d,

Table 8. (cont.)

							$J_{5,6}$=8Hz, 1H, H-5), 5.9(d, $J_{4,5}$=6Hz, 1H, H-4), 6.2-6.66(br m, 2H, two NH protons, exchange with deuterium oxide), 6.66-7.66(m, 6H, COOPh, dihydropyridinyl H-6).
115	C-4	C_6H_5	O	1624	1704	3353	2.6(t, J=7Hz, 2H, -$\underline{CH_2}$N), 2.83(d, J=5Hz, 3H, N-$\underline{CH_3}$, collapses to a singlet after deuterium oxide exchange), 3.06(m, 2H, dihydropyridinyl -$\underline{CH_2}$-S), 3.66(t, J=7Hz, 2H, S$\underline{CH_2}$$CH_2$N), 4.46(m, 2H, dihydropyridinyl H-2), 5.1-5.6(m, 2H, H-3, H-5), 5.73-6.33(m, 2H, two NH protons, exchange with deuterium oxide), 6.76(d, $J_{5,6}$=8Hz, 1H, H-6), 6.9-7.6(m, 5H, COOPh).
116	C-3	C_6H_5	S	1090	1704	3320	2.66(t, J=7Hz, 2H, -$\underline{CH_2}$N), 2.9(d, J=5Hz, 3H, N-CH_3, collapses to a singlet on deuterium oxide exchange), 3.23(m, 2H, dihydropyridinyl -$\underline{CH_2}$-S), 3.73(t, J=7Hz, 2H, S$\underline{CH_2}$$CH_2$N), 4.43(br d, J=3Hz, 2H,

Table 8. (cont.)

							dihydropyridinyl H-2), 5.34(d, $J_{4,5}$=6Hz of d, $J_{5,6}$=8Hz, 1H, H-5), 5.9(d, $J_{4,5}$=6Hz, 1H, H-4), 6.38(br m, 2H, two NH protons, exchange with deuterium oxide), 6.83(d, $J_{5,6}$=8Hz, 1H, H-6), 7.06-7.66(m, 5H, COOPh).
117	C-4	C_6H_5	S	1090	1720	3360	(CDCl$_3$+D$_2$O) 2.7(t, J=7Hz, 2H, -$\underline{CH_2}$N), 2.93(s, 3H, N-CH$_3$), 3.16(s, 2H, dihydropyridinyl-$\underline{CH_2}$-S), 3.76(t, J=7Hz, 2H, S$\underline{CH_2}$CH$_2$N), 4.49(m, 2H, dihydropyridinyl H-2), 5.2-5.63(m, 2H, H-3, H-5), 6.86(d, $J_{5,6}$=8Hz, 1H, H-6), 6.96-7.66(m, 5H, COOPh).
118	C-3	C_6H_5	NCN	2090	1730	3360	2.73(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.03(d, J=5Hz, 3H, N-$\underline{CH_3}$, collapses to a singlet on deuterium oxide exchange), 3.4(s, 2H, dihydropyridinyl-$\underline{CH_2}$-S), 3.8(t, J=7Hz, S$\underline{CH_2}$CH$_2$N), 4.56(distorted d, J=3Hz, 2H, dihydropyridinyl H-2), 5.46(d, $J_{4,5}$=6Hz of d, $J_{5,6}$=8Hz, 1H, H-5), 6.0(d, $J_{4,5}$=6Hz, 1H, H-4), 6.3-6.7(br m, 2H, two NH protons, exchange with

Table 8. (cont.)

							deuterium oxide), 6.93(d, $J_{5,6}$=8Hz, 1H, H-6), 7.16-7.66(m, 5H, COOPh).
119	C-4	C_6H_5	NCN	2168	1704	3384	2.73(t, J=7Hz, 2H, -$\underline{CH_2}$N), 2.96(t, J=5Hz, 3H, NCH_3, collapses to a singlet after deuterium oxide exchange), 3.13(s, 2H, dihydropyridinyl -$\underline{CH_2}$-S), 3.8(t, J=7Hz, S$\underline{CH_2}$$CH_2$N), 4.51(m, 2H, dihydropyridinyl H-2), 5.2-5.63(m, 2H, H-3, H-5), 5.83-6.4(m, 2H, two NH protons, exchange with deuterium oxide), 6.86(d, $J_{5,6}$=8Hz, 1H, H-6), 6.93-7.63(m, 5H, COOPh).
120	C-3	t-C_4H_9	O	1660	1710	3360	1.5(s, 9H, O-t-$\underline{Bu}$), 2.7(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.0(d, J=5Hz, 3H, NCH_3, collapses to a singlet after deuterium oxide exchange), 3.2(s, 2H, dihydropyridinyl -$\underline{CH_2}$-S), 3.8(t, J=7Hz, S$\underline{CH_2}$$CH_2$N), 4.33(br s, 2H, dihydropyridinyl H-2), 5.18(d, $J_{4,5}$=6Hz of d, $J_{5,6}$=8Hz, 1H, H-5), 5.83(d, $J_{4,5}$=6Hz, 1H, H-4), 6.26-6.93(m, 3H, dihydro-

Table 8. (cont.)

							pyridinyl H-6, two NH protons, exchange with deuterium oxide).
121	C-4	t-C_4H_9	O	1650	1710	3360	1.5(s, 9H, O-t-$\underline{Bu}$), 2.7(t, J=7Hz, 2H, -$\underline{CH}_2$N), 3.0(d, J=5Hz, 3H, N-$\underline{CH}_3$, collapses to a singlet after deuterium oxide exchange), 3.13(s, 2H, dihydropyridinyl-$\underline{CH}_2$-S-), 3.86(t, J=7Hz, S$\underline{CH}_2$$CH_2$N), 4.33(d, J=3Hz, 2H, dihydropyridinyl H-2), 5.0-5.6(m, 2H, H-3, H-5), 6.0-6.6(m, 2H, two NH protons, exchange with deuterium oxide) 6.8(d, $J_{5,6}$=8Hz, 1H, H-6).
122	C-3	t-C_4H_9	S	1096	1704	3320	1.53(s, 9H, O-t-$\underline{Bu}$), 2.7(t, J=7Hz, 2H, -$\underline{CH}_2$N), 3.03(d, J=5Hz, 3H, N-$\underline{CH}_3$, collapses to a singlet after deuterium oxide exchange), 3.23(br s, 2H, dihydropyridinyl-$\underline{CH}_2$-S), 3.8(t, J=7Hz, S$\underline{CH}_2$$CH_2$N), 4.36(br s, 2H, dihydropyridinyl H-2), 5.10(d, $J_{4,5}$=6Hz of d, $J_{5,6}$=8Hz, 1H, H-5). 5.86(d, $J_{4,5}$=6Hz, 1H, H-4), 6.4-6.85(m, 3H,

Table 8. (cont.)

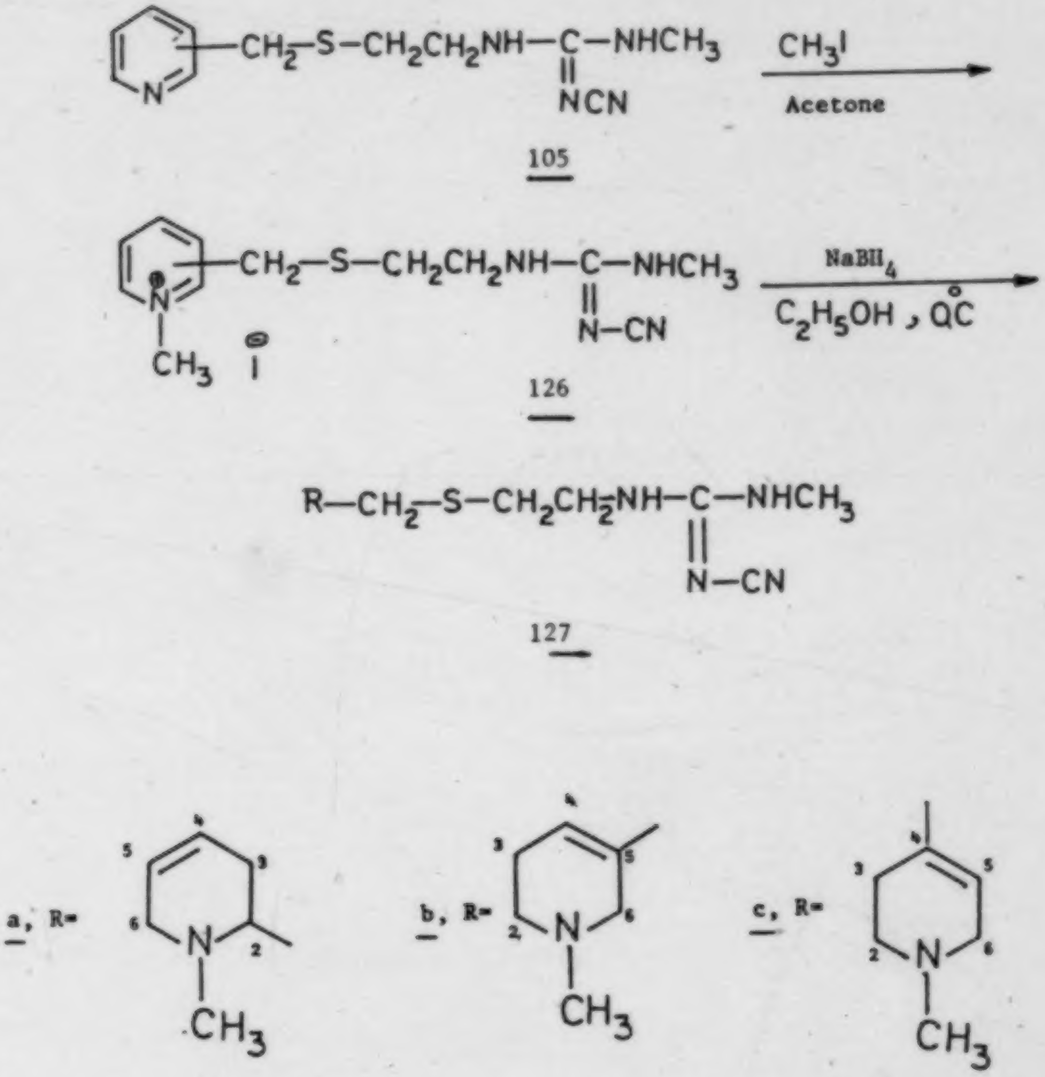
							dihydropyridinyl H-6, two NH protons, exchange with deuterium oxide).
123	C-4	$t\text{-}C_4H_9$	S	1090	1710	3340	1.5(s, 9H, O-t-$\underline{Bu}$), 2.76(t, J=7Hz, 2H, $-\underline{CH}_2N$), 3.06(d, J=5Hz, 3H, $N\text{-}CH_3$, collapses to a singlet on deuterium oxide exchange), 3.2(s, 2H, dihydropyridinyl-$\underline{CH}_2$-S), 3.8(t, J=7Hz, S-$\underline{CH}_2CH_2N$), 4.4(d, J=3Hz, 2H, dihydropyridinyl H-2), 5.0-5.6 (m, 2H, H-3, H-5), 6.1-6.66(m, 2H, two NH protons, exchange with deuterium oxide, 6.86(d, $J_{5,6}$=8Hz, 1H, H-6).
124	C-3	$t\text{-}C_4H_9$	NCN	2168	1704	3384	1.53(s, 9H, O-t-$\underline{Bu}$), 2.7(t, J=7Hz, 2H, $-\underline{CH}_2N$), 3.0(d, J=5Hz, 3H, $N\text{-}CH_3$, collapses to a singlet after deuterium oxide exchange), 3.23(s, 2H, dihydropyridinyl-$\underline{CH}_2$-S), 3.83(t, J=7Hz, S$\underline{CH}_2CH_2N$), 4.36(br s, 2H, dihydropyridinyl H-2), 5.18(d, $J_{4,5}$=6Hz of d, $J_{5,6}$=8Hz, 1H, H-5), 5.86(d, $J_{4,5}$=6Hz, 1H, H-4), 6.33-6.8(m, 3H,

Table 8. (cont.)

							dihydropyridinyl H-6, two NH protons, exchange with deuterium oxide).
125	C-4	t-C_4H_9	NCN	2168	1704	3384	1.5(s, 9H, O-t-$\underline{Bu}$), 2.73(t, J=7Hz, 2H, -$\underline{CH_2}$N), 2.03(d, J=5Hz, 3H, N-CH_3, collapses to a singlet after deuterium oxide exchange), 3.2(s, 2H, dihydropyridinyl-$\underline{CH_2}$-S), 3.86(t, J=7Hz, S$\underline{CH_2}$$CH_2$N), 4.36(d, J=3Hz, dihydropyridinyl H-2) 5.1-5.53(m, 2H, H-3, H-5), 6.2-6.6(m, 2H, two NH protons, exchange with deuterium oxide), 6.83(d, $J_{5,6}$=8Hz, 1H, H-6).

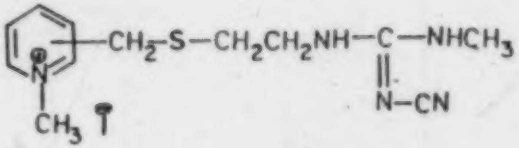
3.4.0.0.0 Synthesis of N"-Cyano-N-methyl-N'-{2-[2-,(5-,4-)(1-methyl-1,2,3,6-tetrahydropyridinyl)methylthio]ethyl}guanidines 127.

The 1-methyl-1,2,3,6-tetrahydropyridinyl analogs 127 a-c were prepared to determine what effect reduction of the pyridinyl ring of 105 and the position of attachment of the side chain had upon H_2-antagonist activity. This study was investigated to gain information regarding interaction of the Het moiety with the histamine H_2-receptor. The iodomethylation of 105 in acetone afforded the N-methyl pyridinium salts 126 in high yield (See Table 9). Reduction of the salts 126 with sodium borohydride in ethanol at 0°C gave the corresponding 1,2,3,6-tetrahydropyridinyl derivatives 127a-c as illustrated in Scheme 5 and summarized in Table 11.


CH₂–S–CH₂CH₂NH–C–NHCH₃
NCN
CH₃I
Acetone
105
NaBH₄
C₂H₅OH , 0°C
126
R–CH₂–S–CH₂CH₂NH–C–NHCH₃
N–CN
127
a, R=
b, R=
c, R=
N
CH₃

Scheme 5. Synthetic Routes used for the Synthesis of N"-Cyano-N-methyl-N'-{2-[2-,(5-,4-)(1-methyl-1,2,3,6-tetrahydropyridinyl) methylthio]ethyl}guanidines 127.

Table 9. Some Physical Data for N"-Cyano-N-methyl-N'-[2-[2-(3-,4-)(1-methylpyridinium)methylthio]ethyl]guanidine Iodides 126.

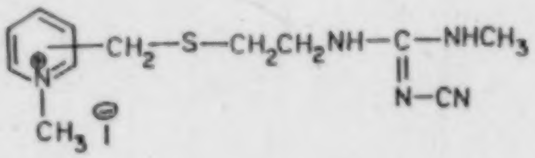


Compd	Point of Attachment	Yield,%	mp,°C	Formula	LRMS[a] Calcd	LRMS[a] Found	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
126a	C-2	72.5	145-148	$C_{12}H_{18}N_5SI$	391.22	391.85	36.85	4.6	17.89	36.98	4.57	17.67
126b	C-3	75	175	$C_{12}H_{18}N_5SI$	391.22	391.85	36.85	4.6	17.89	37.05	4.75	17.90
126c	C-4	87	200	$C_{12}H_{18}N_5SI$	391.22	391.75	36.85	4.6	17.89	36.72	4.67	17.82

---

[a] Low resolution mass spectrum.

Table 10. Infrared (ir) and Proton Magnetic Resonance (^1H nmr) Spectral Data for N"-Cyano-N-methyl-N'-[2-[2-(3-,4-)-(1-methylpyridinium)methylthio]ethyl]guanidine Iodides 126.

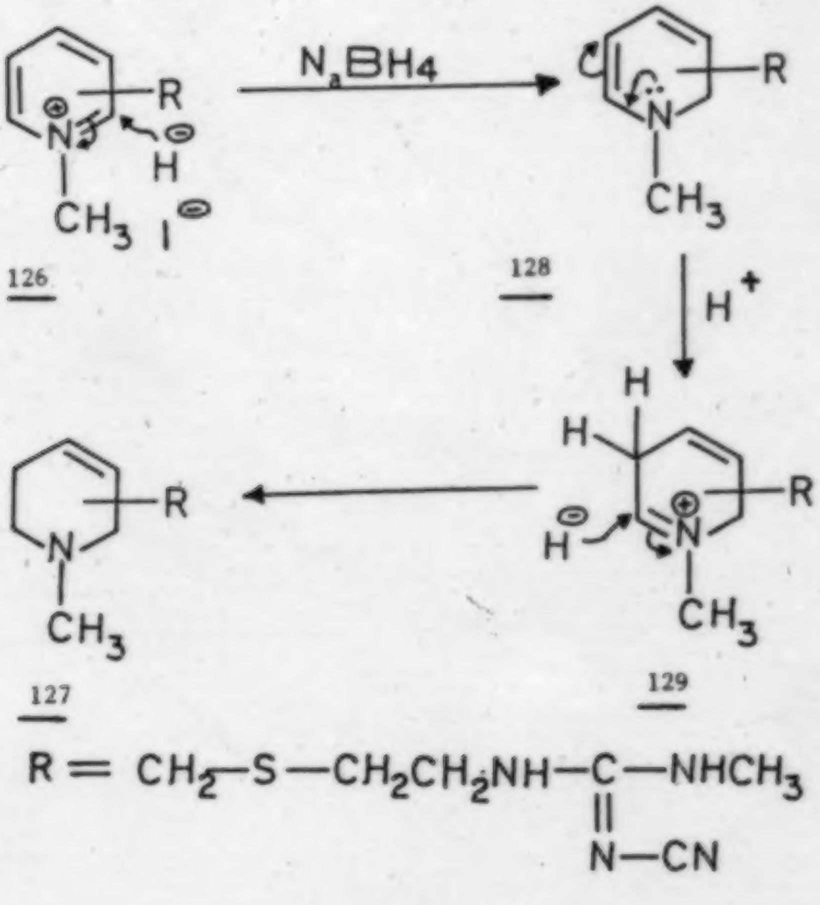


Compd	Point of Attachment	ir, cm^{-1} (KBr) C=N	CN	NH	^1H nmr, δ (DMSO-d_6).
126a	C-2	1580	2180	3280	2.6(t, J=7Hz, 2H, -$\underline{CH_2}$N), 2.75(d, $J_{NH,Me}$=5Hz, 3H, NH$\underline{CH_3}$), 3.3(t, J=7Hz, 2H, S$\underline{CH_2}$CH$_2$N), 4.1(s, 2H, pyridinium-$\underline{CH_2}$S), 4.4(s, 3H, pyridinium N-methyl), 6.45(br s, 2H, two NH protons, exchange with deuterium oxide), 7.1-7.5(m, 2H, H-3, H-5), 7.7(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, H-4), 9.27(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, H-6).

Table 10. (cont.)

126b	C-3	1580	2180	3280	2.7(t, J=7Hz, 2H, $-\underline{CH}_2N$), 2.86(d, $J_{NH,Me}$=5Hz, 3H, $NH\underline{CH}_3$), 3.4(t, J=7Hz, 2H, $S\underline{CH}_2CH_2N$), 4.13(s, 2H, pyridinium-$\underline{CH}_2$-S), 4.6(s, 3H, pyridinium-N-methyl), 6.94(br s, 2H, two NH protons, exchange with deuterium oxide), 8.0-8.4(m, 1H, pyridinium H-5), 8.6-8.96(m, 1H, pyridinium H-4), 9.0-9.6(m, 2H, pyridinium H-2, H-6).
126c	C-4	1580	2180	3280	2.6(t, J=7Hz, 2H, $-\underline{CH}_2N$), 2.66(d, $J_{NH,Me}$=5Hz, 3H, NH-$\underline{CH}_3$), 3.3(t, J=7Hz, 2H, $S\underline{CH}_2CH_2N$), 4.1(s, 2H, pyridinium-$\underline{CH}_2$-S), 4.36(s, 3H, pyridinium N-methyl), 7.04(br s, 2H, two NH protons, exchange with deuterium oxide), 8.13(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyridinium H-3, H-5) 9.0(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyridinium H-2), H-6).

The sodium borohydride reduction of pyridinium salts is still the most efficient synthetic reaction for the preparation of N-substituted-1,2,3,6-tetrahydropyridines. The mechanism for the reduction of pyridinium salts using sodium borohydride has been investigated extensively. It has been reported[147, 148] that attack by hydride anion occurred at carbon adjacent to the quarternary nitrogen to give the 1,2-dihydropyridine intermediate 128 which on protonation and subsequent reduction of the iminium species 129 yielded the 1-methyl-1,2,3,6-tetrahydropyridines 127.



126

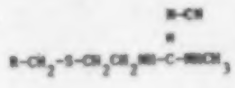
128

129

127

$$R = CH_2{-}S{-}CH_2CH_2NH{-}\underset{\underset{\displaystyle N{-}CN}{\|}}{C}{-}NHCH_3$$

Table 11. Some Physical Data for N"-Cyano-N-methyl-N'-[2-[2-(5-,4-)(1-methyl-1,2,3,6-tetrahydropyridinyl) methylthio]ethyl]guanidines 127



$$R{-}CH_2{-}S{-}CH_2CH_2NH{-}\overset{\overset{\displaystyle N{-}CN}{\|}}{C}{-}NHCH_3$$

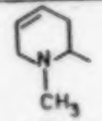
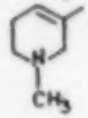
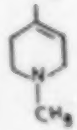
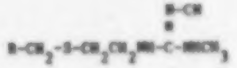
Compd	R	Yield,%	mp, °C	Formula	Exact Calcd	Mass Found
127a		58	oil	$C_{12}H_{21}N_5S$	267.1517	267.1506
127b		50	oil	$C_{12}H_{21}N_5S$	267.1517	267.1515
127c		55	oil	$C_{12}H_{21}N_5S$	267.1517	267.1503

Table 12. Infrared (ir) and Proton Magnetic Resonance (¹H nmr) Spectral Data for N"-Cyano-N-methyl-N'-[2-[2-(5-,4-)[(1-methyl-1,2,3,6-tetrahydropyridinyl)methyl]thio]ethyl]guanidines 127.



$$R{-}CH_2{-}S{-}CH_2CH_2NH{-}\overset{\overset{\displaystyle N{-}CN}{\|}}{C}{-}NHCH_3$$

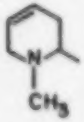
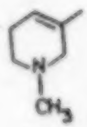
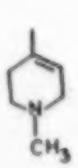
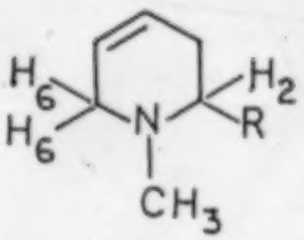
Compd	R	ir, cm^{-1} (KBr)			¹H nmr, δ(CDCl$_3$)
		NH	CN	C=N	
127a		3320	2180	1580	2.22(m, 2H, H-3), 2.30(s, 3H, NMe), 2.7(t, J=7Hz, 2H, -CH_2N), 2.77(m, 2H, -SCH_2CH$_2$), 2.87(d, J=8Hz, 2H, -SCH_2-tetrahydropyridinyl), 2.88(d, $J_{NH,Me}$=5Hz, 3H, NHCH_3, collapses to a singlet after deuterium oxide exchange), 3.1(m, 1H, H-2), 3.45(m, 2H, H-6), 5.7(m, 2H, H-4, H-5), 6.30(broad m, 2H, 2 NH protons, exchange with deuterium oxide).

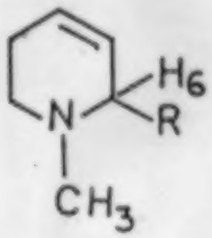
Table 12. (cont.)

127b		3320	2180	1590	2.27(m, 2H, H-5), 2.4(s, 3H, NMe), 2.52(t, J=7Hz, 2H, -$\underline{CH}_2$N), 2.64(t, J=7Hz, 2H, N$\underline{CH}_2$CH$_2$N), 2.9(d, $J_{NH,Me}$=5Hz, 3H, NH$\underline{CH}_3$, collapses to a singlet after deuterium oxide exchange), 3.0(distorted s, 2H, H-6), 3.12(s, 2H, tetrahydropyridinyl -$\underline{CH}_2$-N), 3.4(m, 2H, H-2), 5.64-5.9(m, 2H, H-4, and $\underline{NH}$-Me, exchanges with deuterium oxide), 6.56(br s, 1H, $\underline{NH}$CH$_2$CH$_2$, exchanges with deuterium oxide).
127c		3300	2180	1600	2.3(m, 2H, H-5), 2.6(s, 3H, NMe), 2.61(t, J=7Hz, 2H, -$\underline{CH}_2$N), 2.9(d, $J_{NH,Me}$=5Hz, 3H, NH$\underline{CH}_3$, collapses to a singlet after deuterium oxide exchange), 2.95(t, J=7Hz, N$\underline{CH}_2$CH$_2$N), 3.1-4.2(m, 6H, H-2, H-6, tetrahydropyridinyl -$\underline{CH}_2$-N), 5.63(m, 1H, H-5), 6.26(br s, 2H, two NH protons, exchange with deuterium oxide).

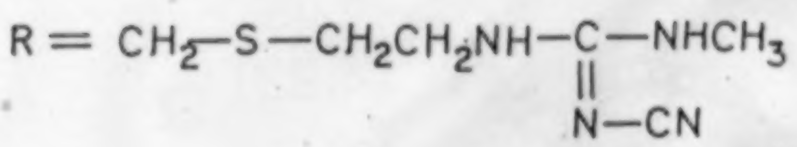
This mechanism has been substantiated by deuterium labelling experiments.[96] The product obtained from the reduction of N"-cyano-N-methyl-N'-{2-[2-(1-methylpyridinium)methylthio]ethyl}guanidine iodide 126a was assigned structure 127a rather than the isomeric structure 130 based on ^1H nmr spectral data for which the chemical shift assignments were verified by double resonance experiments (See Table 11).



127a



130



$$R = CH_2-S-CH_2CH_2NH-\underset{\underset{N-CN}{\|}}{C}-NHCH_3$$

The chemical shift positions for 1,2,3,6-tetrahydropyridinyl hydrogens are well defined.[149-152] The chemical shift positions for the C-2H and C-6H of 127a and 130 are expected to be quite similar but their multiplicity and integration should differ significantly. The degree of shielding for a proton attached to carbon depends in part on the inductive effects of the groups attached to that carbon atom. Therefore H-6 always appears at lower field than the H-2 since H-6 is flanked by both an electronegative ring nitrogen and the C_4-C_5 olefinic group. The H-2 proton which is adjacent only to the ring nitrogen appears at higher field. The 2H multiplet at δ 3.45 was assigned to H-6 and a 1H multiplet at δ 3.1 was assigned to H-2. These assignments are consistent only with structure 127a. If the product was structure 130 the H-6 multiplet at δ 3.45 should have integrated for one hydrogen, while the H-2 multiplet at δ 3.1 should have integrated for two hydrogens and appeared as a triplet ($J_{2,3}$=6-7Hz). The H-2 resonance of unsubstituted 1,2,3,6-tetrahydropyridine always appeared as a triplet.[153] Irradiation of the H-3 protons of 127a indicated coupling to the resonance for the H-2, H-4 and H-5 protons. Irradiation of the H-4 and H-5 protons of 127a also indicated coupling to H-2 and H-3. Similarly, irradiation of the resonance for the H-2 proton of 127a resulted in a simplification of the resonance for the H-4, H-5 and H-3 protons.

The pharmacological test results obtained (See Table 13) suggest the charge distribution in the aromatic pyridine ring system may be important to interaction with the H_2-receptor. The electron density at C-2 < C-4 < C-3 for pyridine and the H_2-antagonistic activity within the isomeric series of thioureas 104 and cyanoguanidines 105 was 2-pyridyl- > 4-pyridyl > 3-pyridyl. This may indicate that an electron rich site on the H_2-receptor interacts with an electron deficient position on the pyridine ring of the H_2-antagonist compound. A group

Table 13. Antagonism of the Histamine Induced Guinea Pig Atria Chronotropic Response.

Compd	H_2-receptor antagonist activity pA_2(±SE)
104a	5.71(0.135)
104b	<4.0
104c	5.04(0.327)
105a	5.05(0.070)
105b	<4.0
105c	4.67(0.112)
109	<4.0
111	<4.0
112	<4.0
113	4.04(0.060)
117	<4.0
118	<4.0
123	<4.0
127a	<4.0[a]
127b	<4.0[a]
127c	<4.0[a]
Cimetidine	6.1[b]

[a] Tested as the oxalate salt.

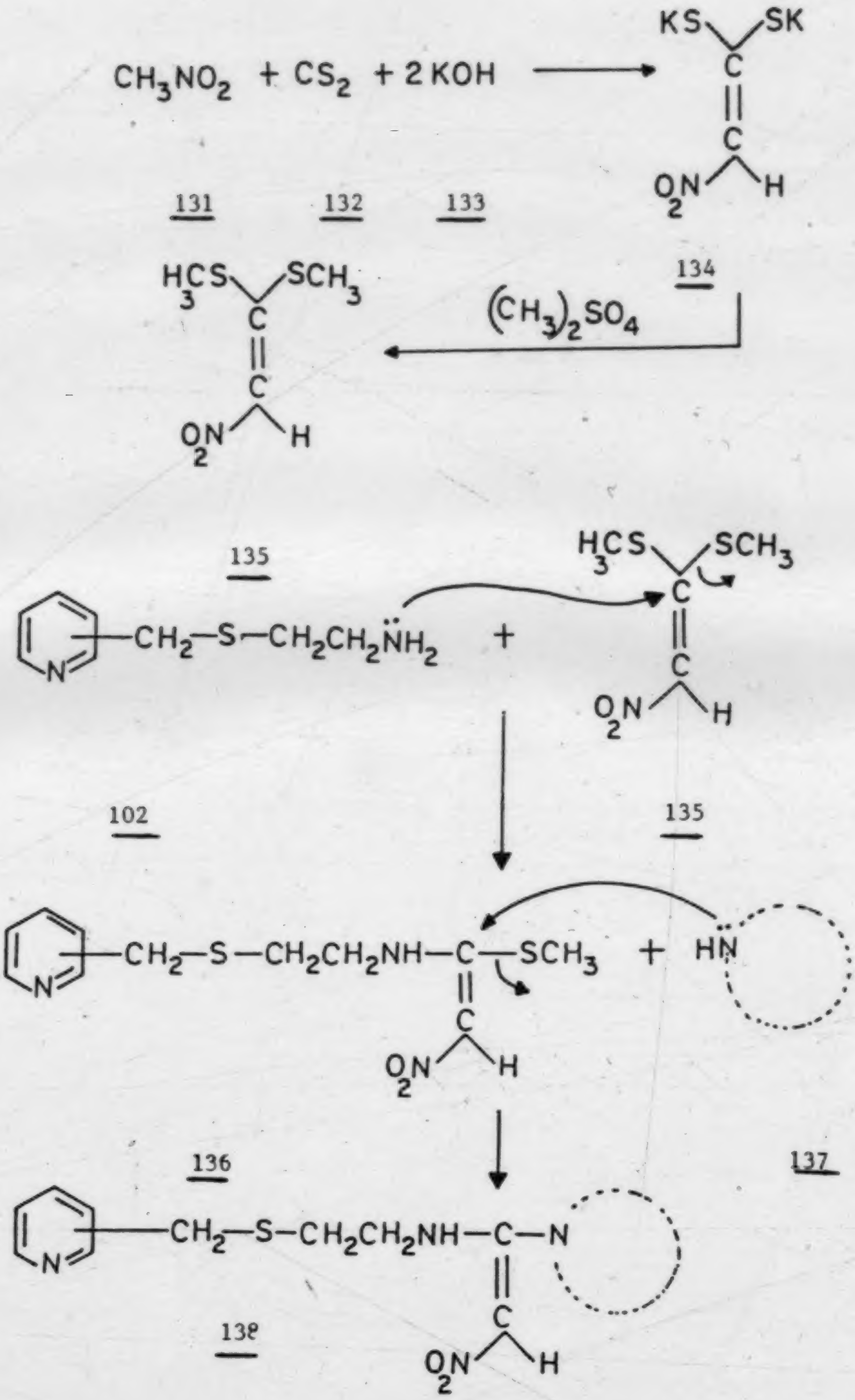
[b] Literature value 154

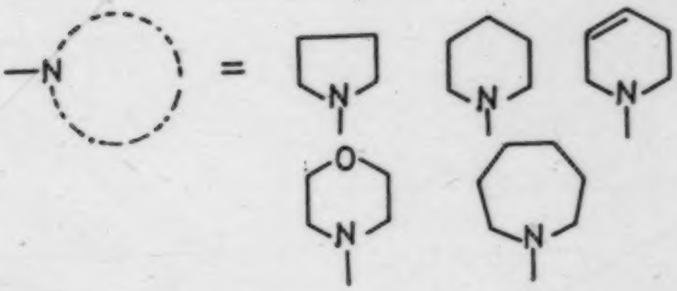
of compounds of general structure 107, which are derivatives of urea, thiourea and cyanoguanidine having a 1,2-dihydropyridinyl ring system, were subsequently prepared to determine whether the 1,2-dihydropyridinyl ring system is bioisosteric to a pyridyl ring with respect to action at H_2-receptors. A comparison of the activities of the urea 109, thiourea 111 and cyanoguanidine derivatives 113 having a 4-(1-methoxycarbonyl-1,2-dihydropyridinyl) ring system indicated that 113 was the most active analog. The urea 109 and thiourea 111 derivatives shifted the histamine dose-response curve marginally at a concentration 10^{-4}M. The 1-methoxycarbonyl 111, 1-phenoxycarbonyl 117 and 1-t-butoxycarbonyl-1,2-dihydropyridinyl 123 analogs were examined to investigate the effect of the substituent attached to the 1,2-dihydropyridinyl nitrogen upon activity. The 1-methoxycarbonyl compound 111 shifted the histamine dose-response curve marginally whereas 117 and 123 exhibited virtually no effect. Although the 1-t-butoxycarbonyl-1,2-dihydropyridinyl analog 123 was inactive in the *in vitro* assay one could expect it to act as a prodrug to the active pyridine analog 104c in the presence of gastric acid when administered orally. It is known that t-butylcarbamate derivatives undergo rapid hydrolysis to the free amine in the presence of mild acid.[155] A comparison of the activities of 112 and 113 indicated that the point of attachment of the 1-methoxycarbonyl-1,2-dihydropyridinyl ring system may be important to activity. The 4-substituted compound 113 was more active than the 3-substituted compound 112 which exhibited no blocking action at a 10^{-4}M concentration. These results parallel those observed for the corresponding pyridine analogs where 105c was more active than

105b. The 1-methyl-1,2,3,6-tetrahydropyridinyl analogs 127a-c were prepared to determine what effect reduction of the pyridinyl ring of 105 and the position of attachment of the side chain had upon H_2-antagonist activity. The *in vitro* test results for compounds 127a-c indicated that they were devoid of H_2-receptor antagonist activity. These results indicate that reduction of the pyridine ring to a 1-methyl-1,2,3,6-tetrahydropyridinyl ring system was not a favourable transformation in relation to interaction of the Het moiety with the histamine H_2-receptor.

3.5.0.0.0 Synthesis of N-[2-Pyridinylmethylthio)ethyl] N' -(cycloalkylamino)-2-nitro-1,1-ethenediamines 138.

The pyridinyl analogs 138 were prepared to investigate the effect which replacement of the 5-dimethylaminomethyl-2-furanyl moiety and the terminal methyl substituent of ranitidine by the respective pyridinyl and cycloalkylamino moieties had upon H_2-receptor antagonist activity. Previous results indicated that replacement of the 5-methyl-4-imidazolyl ring of cimetidine by a pyridinyl ring system resulted in retention of H_2-antagonist activity. It was not known what effect incorporation of a cycloalkylamino moiety would have on the H_2-receptor interaction since the terminal NH proton was no longer present. The synthesis of the target N-[2-(pyridinylmethylthio)ethyl]-N'-(1-cycloalkylamino)-2-nitro-1,1-ethenediamines 138 is outlined in Scheme 6 and the results are summarized in Table 14. Thus reaction of 102 with *bis*-1,1-thiomethyl-2-nitroethene 135 gave the respective N-[2-(pyridinylmethylthio)ethyl]-1-methylthio-2-nitroetheneamines 136. The reaction of 136 with nitrogen nucleophiles 137 as pyrrolidine,

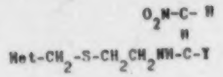

CH_3NO_2 + CS_2 + 2 KOH
$(CH_3)_2SO_4$



a, 2-pyridiyl b, 3-pyridyl c, 4-pyridyl

Scheme 6. Synthetic Routes used for the Synthesis of N-[2-(Pyridinylmethylthio)ethyl]-N'-(cycloalkylamino)-2-nitro-1,1-ethenediamines 138.

Table 14. Some Physical Data for N-[2-[2-(3-,4-)Pyridinylmethylthio]ethyl]-2-nitro-1,1-ethenediamines 138.



$$\overset{O_2N-C-H}{\overset{\|}{Het-CH_2-S-CH_2CH_2NH-C-Y}}$$

Compd	Het	Y	Reaction Time (h)	Rf	%	mp, °C	Formula[b]	Exact Mass Calcd	Exact Mass Found	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
139	2-pyr	$-SCH_3$	48	0.71	70	115	$C_{11}H_{15}N_3O_2S_2$	285.0606	285.0606	—	—	—	—	—	—
140	3-pyr	$-SCH_3$	48	0.70	75	108	$C_{11}H_{15}N_3O_2S_2$	—	—	46.32	5.25	14.72	46.40	5.38	14.90
141	4-pyr	$-SCH_3$	48	0.69	65	165	$C_{11}H_{15}N_3O_2S_2$	—	—	46.32	5.25	14.72	46.49	5.37	14.91
142	2-pyr	1-pyrr[a]	4	0.75	87	131[c]	$C_{14}H_{20}N_4O_2S$	308.1307	308.1303	23.41	3.06	7.79	23.86	3.19	7.76
143	3-pyr	1-pyrr[a]	4	0.70	83	137[c]	$C_{14}H_{20}N_4O_2S$	308.1307	308.1307	23.41	3.06	7.79	23.86	3.19	7.69

Table 14. (cont.)

144	4-pyr	1-pyrr[a]	4	0.76	85	140[c]	$C_{14}H_{20}N_4O_2S$	308.1307	308.1308	23.41	3.06	7.79	23.88	3.27	7.82
145	2-pyr	1-pip[a]	20	0.73	71	132[c]	$C_{15}H_{22}N_4O_2S$	322.1463	322.1455	24.61	3.27	7.65	24.90	3.48	8.20
146	3-pyr	1-pip	20	0.80	79	136[c]	$C_{15}H_{22}N_4O_2S$	322.1464	322.1458	24.61	3.27	7.65	24.69	3.39	7.92
147	4-pyr	1-pip	20	0.77	76	140[c]	$C_{15}H_{22}N_4O_2S$	322.1463	322.1460	24.61	3.27	7.65	24.86	3.40	8.02
148	2-pyr	1-(1,2,3,6-)thp	18	0.66	81	127[c]	$C_{15}H_{20}N_4O_2S$	320.1307	320.1303	24.68	3.01	7.67	24.59	3.39	7.88
149	3-pyr	1-(1,2,3,6-thp	18	0.69	88	130[c]	$C_{15}H_{20}N_4O_2S$	320.1307	320.1303	24.68	3.01	7.67	24.53	3.39	7.89

Table 14. (cont.)

150	4-pyr	1-(1,2, 3, thp	18	0.70	81	135^{c}	$C_{15}H_{20}N_4O_2S$	320.1307	320.1300	24.68	3.01	7.67	24.57	3.43	7.90
151	2-pyr	4-mor	48	0.75	75	114^{c}	$C_{14}H_{20}N_4O_3S$	324.1256	324.1250	22.9	2.99	7.62	23.57	3.05	7.77
152	3-pyr	4-mor	48	0.70	75	120^{c}	$C_{14}H_{20}N_4O_3S$	324.1256	324.1246	22.9	2.99	7.62	23.68	3.09	7.73
153	4-pyr	4-mor	48	0.80	75	125^{c}	$C_{14}H_{20}N_4O_3S$	324.1256	324.1245	22.9	2.99	7.62	23.70	3.06	7.73
154	2-pyr	1-homo-pip	30	0.50	74	123^{c}	$C_{16}H_{24}N_4O_2S$	336.1620	336.1613	25.77	3.48	7.51	25.45	3.92	7.75

Table 14. (cont.)

155	3-pyr	1-homo-pip	30	0.60	79	127[c]	$C_{16}H_{24}N_4O_2S$	336.1620	336.1614	25.77	3.48	7.51	25.78	3.88	7.77
156	4-pyr	1-homo-pip	30	0.65	75	130[c]	$C_{16}H_{24}N_4O_2S$	336.1[d]	336.00	25.77	3.48	7.51	25.75	3.81	6.78

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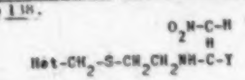
[a] Pyr denotes pyridinyl, pyrr denotes pyrrolidinyl, pip denotes piperidinyl, thp denotes 1-(1,2,3,6-)tetrahydropyridinyl, mor denotes morpholinyl, and homopip denotes homopiperidinyl.

[b] All compounds were analysed as their dihydrogen hexachloroplatinate salts, for C, H, N and/or for C, H, N, O and S using high resolution mass spectrometry.

[c] Dihydrogen hexachloroplatinate salt

[d] Low resolution mass spectrum

Table 15. Infrared (ir) and Proton Magnetic Resonance (^{1}H nmr) Spectral Data for N-{2-[2-(3-,4-)Pyridinyl-methylthio]ethyl}-2-nitro-1,1-ethenediamines 138.



$$\text{Het-CH}_2\text{-S-CH}_2\text{CH}_2\text{NH-}\overset{\displaystyle \text{O}_2\text{N-C-H} \atop \|}{\text{C}}\text{-Y}$$

			ir, cm^{-1} (KBr)		
Compd	Het	Y	NO$_2$	NH	^{1}H nmr, δ(CDCl$_3$)
139	2-pyridinyl	-SCH$_3$	1500	3350	2.55(s, 3H, S-$\underline{\text{CH}_3}$), 2.93(t, J=7Hz, 2H, -$\underline{\text{CH}_2}$N), 3.69(t, J=7Hz, 2H, S$\underline{\text{CH}_2}$CH$_2$N), 4.01(s, 2H, pyr^a-$\underline{\text{CH}_2}$-S), 6.66(s, 1H, $\underline{\text{CH}}$NO$_2$), 7.13-7.63(complex m, 2H, pyr^a H-3, H-5), 7.81(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-4), 8.68(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-6), 10.58(br s, 1H, NH, exchanges with deuterium oxide).
140	3-pyridinyl	-SCH$_3$	1500	3350	2.42(s, 3H, S$\underline{\text{CH}_3}$), 2.75(t, J=7Hz, 2H, -$\underline{\text{CH}_2}$N), 3.60(t, J=7Hz, 2H, S$\underline{\text{CH}_2}$CH$_2$N), 3.63(s, 2H, pyr^a-$\underline{\text{CH}_2}$-S), 6.56(s,

Table $\underline{15}$. (cont.)

					1H, $\underline{CH}NO_2$), 7.15-7.36(m, 1H, pyr* H-5), 7.59-7.83(m, 1H, pyr* H-4), 8.39-8.62(m, 2H, pyr* H-2, H-6), 10.55(br s, 1H, NH, exchanges with deuterium oxide).
$\underline{141}$	4-pyridinyl	$-SCH_3$	1500	3350	2.09(s, 3H, $S\underline{CH_3}$), 2.36(t, J=7Hz, 2H, $\underline{CH_2}N$), 3.16(t, J=7Hz, 2H, $S\underline{CH_2}CH_2N$), 3.4(s, 2H, pyr*-$\underline{CH_2}$-S), 6.2(s, 1H, $\underline{CH}NO_2$), 6.95(d, $J_{2,3}=J_{5,6}=6$Hz, 2H, pyr* H-3, H-5), 8.2(d, $J_{2,3}=J_{5,6}=6$Hz, 2H, pyr* H-2, H-6) 10.4-11.0(br s, 1H, NH, exchanges with deuterium oxide).
$\underline{142}$	2-pyridinyl	1-pyrrolidinyl	1500	3350	1.8-2.33(br m, 4H, pyrrolidinyl H-3, H-4), 2.75(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.1-3.8(m, 6H, $S\underline{CH_2}CH_2N$, pyrrolidinyl H-2, H-5), 3.88(s, 2H, pyr*-$\underline{CH_2}S$), 6.6(s, 1H, $\underline{CH}NO_2$), 7.06-7.6(complex m, 2H, pyr* H-3 and H-5), 7.8(d, $J_{3,4}=8$Hz of d, $J_{4,5}=8$Hz of d, $J_{4,6}=2$Hz, 1H, pyr* H-4), 8.58(d, $J_{5,6}=5$Hz of d, $J_{4,6}=2$Hz, 1H, pyr* H-6), 10.16(br s, 1H, NH, exchanges with deuterium oxide).

Table 15. (cont.)

143	3-pyridinyl	1-pyrrolidinyl	1500	3350	1.6-2.33(br m, 4H, pyrrolidinyl H-3 and H-4), 2.78(t, J=7Hz, 2H, $-\underline{CH}_2N$), 3.13-3.76(m, 6H, $S\underline{CH}_2CH_2N$, pyrrolidinyl H-2 and H-5), 3.83(s, 2H, pyr[a]$-\underline{CH}_2-S$), 6.63(s, 1H, $\underline{CH}NO_2$), 7.16-7.5(m, 1H, pyr[a] H-5), 7.8(d, $J_{4,5}$=8Hz, 1H, pyr[a] H-4), 8.33-8.76(m, 2H, pyr[a] H-2 and H-6), 9.98(br s, 1H, NH, exchanges with deuterium oxide).
144	4-pyridinyl	1-pyrrolidinyl	1500	3350	1.6-2.43(br m, 4H, pyrrolidinyl H-3 and H-4), 2.81(t, J=7Hz, 2H, $-\underline{CH}_2N$), 3.1-3.76(m, 6H, $S\underline{CH}_2CH_2N$, pyrrolidinyl H-2 and H-5), 3.88(s, 2H, pyr[a] $-\underline{CH}_2-S$), 6.63(s, 1H, $\underline{CH}NO_2$), 7.43(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyr[a] H-3 and H-5), 8.65(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyr[a] H-2 and H-6), 10.08(br s, 1H, NH, exchanges with deuterium oxide).
145	2-pyridinyl	1-piperidinyl	1500	3350	1.33-1.93(br m, 6H, piperidinyl H-3, H-4 and H-5),

Table 15. (cont.)

					2.76(t, J=7Hz, $-\underline{CH_2}N$), 3.0-3.73(br m, 6H, $S\underline{CH_2}CH_2N$ and piperidinyl H-2, H-6), 3.9(s, 2H pyr^a $-\underline{CH_2}-S$), 6.49(s, 1H, $\underline{CH}NO_2$), 7.06-7.56(complex m, 2H, pyr^a H-3 and H-5), 7.74(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d $J_{4,6}$=2Hz, 1H, pyr^a H-4), 8.54(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-6), 9.54(br s, 1H, NH, exchanges with deuterium oxide).
146	3-pyridinyl	1-piperidinyl	1500	3350	1.43-1.89(br m, 6H, piperidinyl H-3, H-4, H-5), 2.73(t, J=7Hz, $-\underline{CH_2}N$), 3.0-3.66(br m, 6H, $S\underline{CH_2}CH_2N$, piperidinyl H-2, H-6), 3.81(s, 2H, pyr^a $-\underline{CH_2}-S$), 6.4(s, 1H, $\underline{CH}NO_2$), 7.13-7.5(m, 1H, pyr^a H-5), 7.8(d, $J_{4,5}$=8Hz, 1H, pyr^a H-4) 8.33-8.88(m, 2H, pyr^a H-2, H-6), 9.64(br s, 1H, NH, exchanges with deuterium oxide).
147	4-pyridinyl	1-piperidinyl	1500	3350	1.33-1.9(m, 6H, piperidinyl H-3, H-4, H-5), 2.76(t, J=7Hz, 2H, $-\underline{CH_2}N$), 2.96-3.7(complex m, 6H, $S\underline{CH_2}CH_2N$, piperidinyl H-2 and H-6), 3.8(s, 2H, pyr^a $-\underline{CH_2}-S$).

Table 15. (cont.)

					6.53(s, 1H, $\underline{CH}NO_2$), 7.39(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^a H-3 and H-5), 8.63(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^a H-2 and H-6), 9.83(br s, 1H, NH, exchanges with deuterium oxide).
148	2-pyridinyl	1-(1,2,3,6-tetrahydropyridinyl	1500	3350	2.25(m, 2H, 1,2,3,6-tetrahydropyridinyl H-3), 2.75(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.1-3.83(complex m, 6H, S$\underline{CH_2}$CH$_2$N, 1,2,3,6-tetrahydropyridinyl H-2, H-6), 3.91(s, 2H, pyr^a-$\underline{CH_2}$-S), 5.83(m, 2H, tetrahydropyridinyl H-4 and H-5), 6.5(s, 1H, $\underline{CH}NO_2$), 7.0-7.5(complex m, 2H, pyr^a H-3, H-5), 7.71(d, $J_{3,4}=8Hz$ of d, $J_{4,5}=8Hz$ of d, $J_{4,6}=2Hz$, 1H, pyr^a H-4), 8.49(d, $J_{5,6}=5Hz$ of d, $J_{4,6}=2Hz$, 1H, pyr^a H-6), 8.73-9.8(br m, 1H, NH, exchanges with deuterium oxide).
149	3-pyridinyl	1-(1,2,3,6,tetrahydropyridinyl	1500	3350	2.36(m, 2H, tetrahydropyridinyl H-3), 2.84(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.1-3.86(complex m, 6H, S$\underline{CH_2}$CH$_2$N, tetrahydropyridinyl H-2, H-6) 3.93(s, 2H, pyr^a -$\underline{CH_2}$-S), 5.91(m, 2H, tetrahydropyridinyl H-4 and H-5), 6.6(s, 1H, $\underline{CH}NO_2$),

Table 15. (cont.)

					7.23-7.59(m, 1H, pyr^{a} H-5), 7.6-8.0(m, 1H, pyr^{a} H-4), 8.33-8.86(m, 2H, pyr^{a} H-2, H-6), 9.66(br s, 1H, NH, exchanges with deuterium oxide).
150	4-pyridinyl	1-(1,2,3,6-tetrahydropyridinyl	1500	3350	2.23(m, 2H, tetrahydropyridinyl H-3), 2.71(t, J=7Hz, 2H, -$\underline{CH}_2$N), 3.0-4.0(complex m, 8H, pyr^{a} -$\underline{CH}_2$-S, S$\underline{CH}_2$CH$_2$N and tetrahydropyridinyl H-2, H-6), 5.79(m, 2H, tetrahydropyridinyl H-4, H-5), 6.5(s, 1H, $\underline{CH}$NO$_2$), 7.29(d, $J_{2,3}$=$J_{5,6}$=6Hz, 2H, pyr^{a} H-3 and H-5), 8.55(d, $J_{2,3}$=$J_{5,6}$=6Hz, 2H, pyr^{a} H-2 and H-6), 8.66-10.33(br m, 1H, NH, exchanges with deuterium oxide).
151	2-pyridinyl	4-morpholinyl	1500	3350	2.31(t, J=7Hz, 4H, morpholinyl H-3, H-5), 2.73(t, J=7Hz, 2H, -$\underline{CH}_2$N), 3.03(t, J=7Hz, 4H, morpholinyl H-2, H-6), 3.2-3.53(m, 4H, pyr^{a} -$\underline{CH}_2$-S and S$\underline{CH}_2$CH$_2$N), 6.13(s, 1H, $\underline{CH}$NO$_2$), 6.76-7.26(complex m, 2H, pyr^{a} H-3 and H-5), 7.46(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^{a}

Table 15. (cont.)

					H-4), 8.34(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-6), 9.36(br s, 1H, NH, exchanges with deuterium oxide).
152	3-pyridinyl	4-morpholinyl	1500	3350	2.88(t, J=7Hz, 4H, morpholinyl H-3, H-5), 3.33(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.61(t, J=7Hz, 4H, morpholinyl H-2, H-6), 3.76-4.06(m, 4H, pyr^a $-\underline{CH_2}-S$ and $S\underline{CH_2}CH_2N$), 6.6(s, 1H, $\underline{CH}NO_2$), 7.43(d, $J=_{4,5}$=8Hz of d, $J_{5,6}$=4Hz, 1H, pyr^a H-5), 7.9(d, $J_{4,5}$=8Hz of d, $J_{4,6}$=4Hz, 1H, pyr^a H-4), 8.56-8.83(m, 2H, pyr^a H-2, H-6), 9.83(br s, 1H, NH, exchanges with deuterium oxide).
153	4-pyridinyl	4-morpholinyl	1500	3350	2.59(t, J=7Hz, 4H, morpholinyl H-3 and H-5), 3.05(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.35(t, J=7Hz, 4H, morpholinyl H-2 and H-6), 3.5-3.83(m, 4H, pyr^a $-\underline{CH_2}-S$ and $S\underline{CH_2}CH_2N$), 6.43(s, 1H, $\underline{CH}NO_2$), 7.31(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyr^a H-3 and H-5), 8.61(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyr^a H-2, H-6).

Table 15. (cont.)

					9.6(br s, 1H, NH, exchanges with deuterium oxide).
154	2-pyridinyl	1-homopiperidinyl	1500	3350	1.33-2.03(br m, 8H, homopiperidinyl H-3 to H-6), 2.75(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.1-3.76(m, 6H, S$\underline{CH_2}$CH$_2$N, homopiperidinyl H-2 and H-7), 3.88(s, 2H, pyr^a -$\underline{CH_2}$-S), 6.56(s, 1H, $\underline{CH}$NO$_2$), 7.0-7.53(complex m, 2H, pyr^a H-3, H-5), 7.71(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-4), 8.5(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-6), 9.33(br s, 1H, NH, exchanges with deuterium oxide).
155	3-pyridinyl	1-homopiperidinyl	1500	3350	1.43-2.1(complex m, 8H, 1-homopiperidinyl H-3 to H-6), 2.7(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.2-3.63(m, 6H, S$\underline{CH_2}$CH$_2$N, homopiperidinyl H-2 and H-7), 3.79(s, 2H, pyr^a -$\underline{CH_2}$-S), 6.6(s, 1H, $\underline{CH}$NO$_2$), 7.33(d, $J_{4,5}$=8Hz of d, $J_{5,6}$=4Hz, 1H, pyr^a H-5), 7.8(d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a

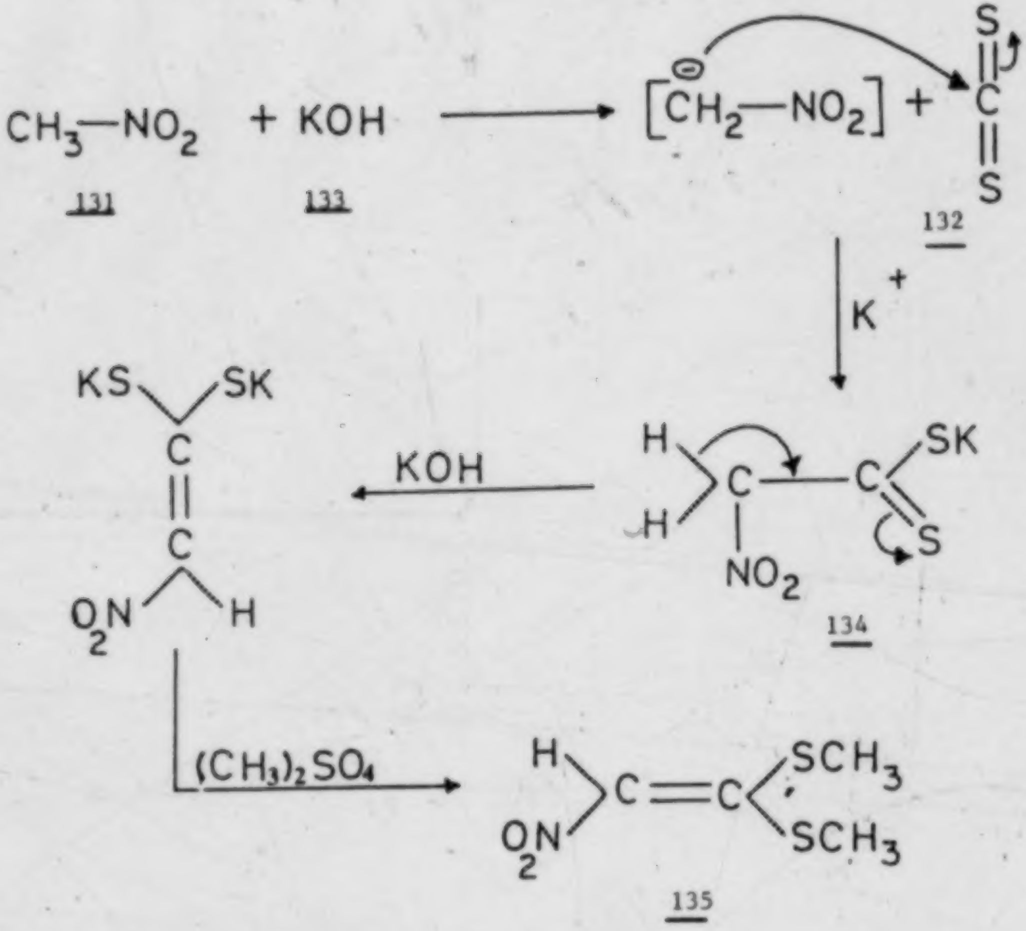
Table 15. (cont.)

					H-4), 8.43-8.73(m, 2H, pyr[a] H-2, H-6), 9.43(br s, 1H, NH, exchanges with deuterium oxide).
156	4-pyridinyl	1-homopiperidinyl	1500	3350	1.5-2.0(complex m, 8H, homopiperidinyl H-3 to H-6), 2.74(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.22-3.70(m, 6H, S$\underline{CH_2}$CH$_2$, homopiperidinyl H-2 and H-7), 3.75(s, 2H, pyr[a] -$\underline{CH_2}$-S), 6.6(s, 1H, $\underline{CH}$NO$_2$), 7.3(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyr[a] H-3 and H-5), 8.55(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyr[a] H-2 and H-6), 9.45(br s, 1H, NH, exchanges with deuterium oxide).

---

[a] pyr denotes pyridine

piperidine, 1-(1,2,3,6-tetrahydropyridine), morpholine and homopiperidine provided 136 in good yield (See Table 14). The 2-nitro-1,1-ethenediamines 142, 144, 150, 154, 156 were studied to determine the effect which a pyridinyl ring, the pyridinyl substituent position and incorporation of the terminal N'-nitrogen atom into a pyrrolidine, 1,2,3,6-tetrahydropyridine and homopiperidine ring system has upon H_2-antagonistic activity. Neither the 2-pyridinyl 142 or 4-pyridinyl 144 compounds exhibited any shift in the histamine dose-response curve at a concentration of 10^{-4} molar. This lack of activity is most likely due to the 1-pyrrolidino group since the corresponding 2-pyridinyl 154 and 4-pyridinyl 156 analogs having a 1-homopiperidinyl group exhibited pA_2 values of 5.26 and 4.53 respectively. The observation that 154 was more potent than 156 is consistent with some earlier results which showed the relative activities within an isomeric series of thiourea and cyanoguanidine compounds was 2-pyridyl > 4-pyridyl > 3-pyridyl.[315] A comparison of the activities exhibited by 144, 150 and 156 indicated the effect of ring size, for the cycloalkylamino substituent Y, upon H_2-antagonist activity. The relative order of H_2-antagonist activity was 1-homopiperidinyl > 1-(1,2,3,6-tetrahydropyridinyl) > 1-pyrrolidinyl. The ir and ^1H nmr spectroscopic data for compounds 139-156 are summarized in Table 15. The mechanism suggested for the formation of bis-1,1-thiomethyl-2-nitroethene 135 prepared from nitromethane is illustrated below (See Scheme 6).


CH_3-NO_2
+ KOH
131
133
$[\overset{\ominus}{C}H_2-NO_2]$ +
S=C=S
132
K^+
KS
SK
O_2N
H
KOH
H
H
SK
S
NO_2
134
$(CH_3)_2SO_4$
H
O_2N
SCH_3
SCH_3
135

The structure assigned to N-[2-(pyridinylmethylthio)ethyl]-1-

methylthio-2-nitroetheneamine 139 was consistent with the ir, ^{1}H nmr and mass spectral data. The ir spectrum revealed the presence of an NH group at 3350 and a NO_2 group at 1500 cm^{-1}. The ^{1}H nmr spectrum in deuterochloroform (δ) exhibited a 3H singlet at 2.55 assigned to $-S\underline{CH_3}$, a 2H triplet (J=7Hz) at 2.93 due to $-\underline{CH_2}N$, a 2H triplet (J=7Hz) at 3.69 attributed to $S\underline{CH_2}CH_2N$, a 2H singlet at 4.01 assigned to 2-pyridinyl-$\underline{CH_2}$-S, a 1H singlet at 6.66 due to $\underline{CH}NO_2$, a 2H complex multiplet at 7.13-7.63 for the pyridinyl H-3 and H-5 protons, a 1H doublet ($J_{3,4}$= 8Hz) of doublet ($J_{4,5}$=8Hz) of doublet ($J_{4,6}$=2Hz) at 7.81 assigned to the 2-pyridinyl H-4, a 1H doublet ($J_{5,6}$=5Hz) of doublet ($J_{4,6}$=2Hz) at 8.68 due to the pyridinyl H-6 and a 1H broad singlet at 10.58 attributed to the NH which exchanged with deuterium oxide. The structure assigned to 154 was also consistent with the ir, ^{1}H nmr, mass spectral data and microelemental analysis. The ir spectrum revealed the presence of an NH at 3350 and a NO_2 group at 1500 cm^{-1}. The ^{1}H nmr spectrum (δ) in deuterochloroform exhibited a complex 8H broad multiplet at 1.33-2.03 assigned to the homopiperidinyl H-3 to H-6, a 2H triplet (J=7Hz) at 2.75 for the $-\underline{CH_2}N$, a 6H multiplet at 3.1-3.76 due to $S\underline{CH_2}CH_2N$ and homopiperidinyl H-2 and H-7, a 2H singlet at 3.88 attributed to the pyridinyl-$\underline{CH_2}$-S, a 1H singlet at 6.56 assigned to $\underline{CH}NO_2$, a 2H complex multiplet at 7.0-7.53 due to the pyridinyl H-3, H-5, a 1H doublet ($J_{3,4}$=8Hz) of doublet ($J_{4,5}$=8Hz) of doublet ($J_{4,6}$=2Hz) at 7.71 due to the pyridinyl H-4, a 1H doublet ($J_{5,6}$=5Hz) of doublet ($J_{4,6}$=2Hz) at 8.5 for the pyridinyl H-6 and a 1H broad singlet at 9.33 assigned to the NH which exchanges with deuterium oxide. The microanalytical and mass spectral data were also consistent with the assigned structure (See Table 14).

3.6.0.0.0 Application of a Nuclear Overhauser Enhancement (NOE) Difference Experiment for Determination of the Molecular Configuration of N-[2-Pyridinylmethylthio)ethyl]N'-(cycloalkylamino)-2-nitro-1, 1-ethenediamines 138.

The Nuclear Overhauser Effect (NOE) induces a change in the integrated nuclear magnetic resonance (NMR) absorption intensity of a nuclear spin when the NMR resonance of another spin is saturated. The spins involved may be either heteronuclear or chemically shifted homonuclear spins. The term "Overhauser Effect" referred originally to the dynamic polarization of nuclei in metals[156] when the spin resonance of the electrons were saturated. The first application of this effect in a system having only nuclear spins was performed by Solomon and Bloembergen[157] in their study of chemical exchange in HF. The Nuclear Overhauser Effect (NOE) next found application for the assignment of complex nuclear magnetic resonance (NMR) spectra[158] for chemical exchange studies,[159] nuclear relaxation[160] and for signal-to-noise enhancement in NMR spectrometry.[161] The potential use of NOE for providing information on the conformation and configuration of molecules in solution was first demonstrated by Anet and Bourn.[162] This technique now finds extensive application in NMR spectrometry. Recently, Bell and Saunders reported a direct correlation between NOE enhancement and internuclear distances.[163] Schirmer, Noggle, Davis and Hart have demonstrated that relative internuclear distances can be determined quantitatively from NOE measurements for systems containing three or more spins.[164] The latter study in particular indicated that an understanding of nuclear spin-lattice relaxation provided more information from an NOE experiment than is otherwise available.

The 300 MHz ^1H nmr spectrum ($CDCl_3$, δ) of 156 exhibited a sharp singlet at 6.6 indicating that a single stereochemistry existed about the C=CH-NO_2 olefinic bond. Some Nuclear Overhauser Enhancement (NOE) difference ^1H nmr experiments were therefore carried out to investigate the stereochemistry of 156 to determine whether the homopiperidinyl ring system was *cis* or *trans* to the hydrogen of the C=CH-NO_2 group. When the H-3 and H-6 protons of the homopiperidinyl ring at δ 1.75 for 156 were irradiated a positive NOE peak at δ 3.3 (5.04%) for H-2 and H-7 of the homopiperidinyl was observed. When the C=CH- NO_2 peak at δ 6.6 was irradiated positive NOE peaks at δ 3.33 (2.07%) for H-2 and H-7 and at δ 1.75 (0.75%) for H-3 and H-6 of the homopiperidinyl ring were present. The results of this experiment are not unambiguous since the % NOE is small and only one stereochemical isomer was available for the study. These results, however, suggest that the homopiperidinyl ring system is *cis* to the olefinic hydrogen of 156. If this is so, compound 136 would have the stereochemistry shown in Scheme 6 and reaction of 102 with 135 would have resulted in displacement of the thiomethyl substituent of 135 *cis* to the nitro group to yield 136 The regiospecificity of this nucleophilic reaction could be due to an interaction between the amino group of 102 and the nitro group of 135 which directs the displacement of the thiomethyl group *cis* to the nitro moiety. Spectroscopic studies [165] on ranitidine 9e indicated that the nitroethene dialkylamine group in both the base and hydrochloride existed predominately, if not completely, in the enediamine tautomeric form as shown in Fig 5. There was a low barrier to rotation about the carbon-carbon double bond at 271°K. The energy barrier to rotation is influenced, at least in part, by intramolecular hydrogen bonding between the nitro and amino groups. In strongly acid solution C-protonation with charge delocalisation occurred on the enediamine with consequent loss of conjugation. At 271°K two sets of resonances were observed[165] for all the protons associated with the dialkylaminonitroethene group. The measured coalescence temperature Tc at

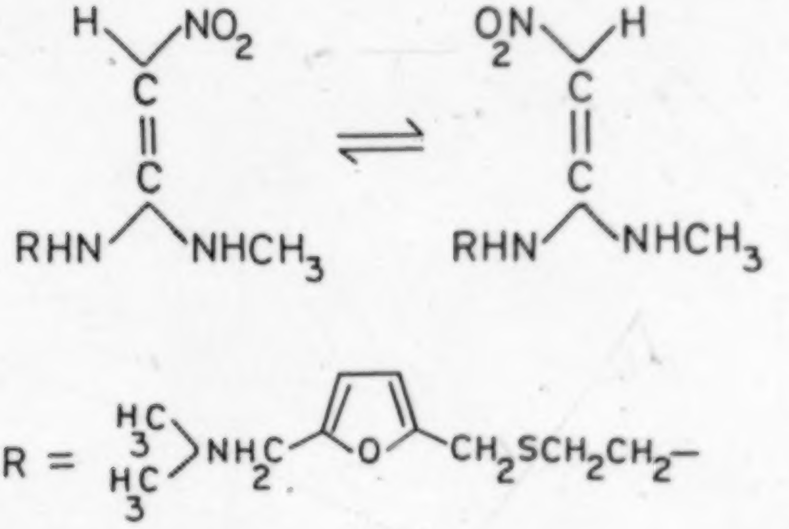

H
NO2
C
C
RHN
NHCH3
O2N
H
C
C
RHN
NHCH3
R =
H3C
H3C
NH2C
O
CH2SCH2CH2—

Figure 5. Enediamine Tautomeric Form of Ranitidine 9e.

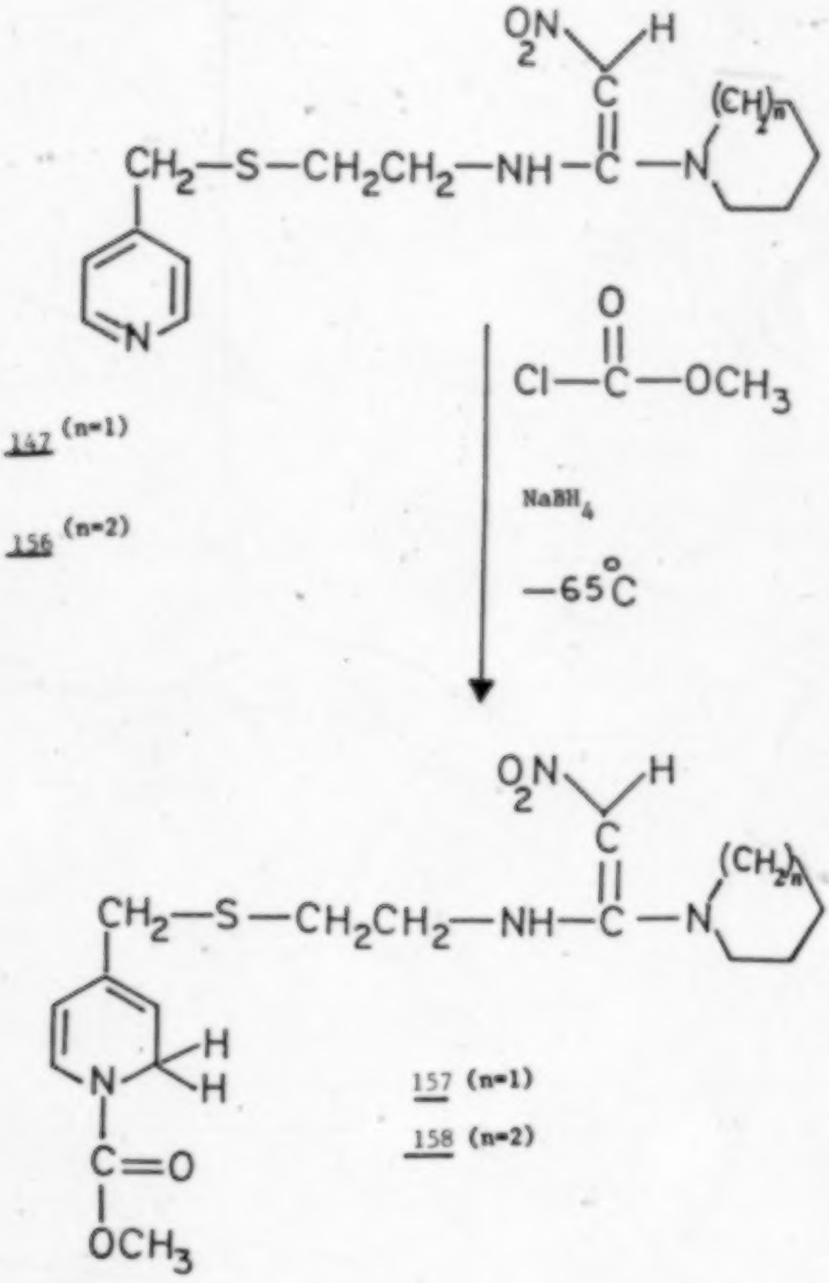
250.13 MHz for the $NHCH_3$ signals was 314°K and the energy barrier to rotation as given by the difference in Gibbs free energy $\Delta G^{\ddagger}$ is 15.7 ± 0.1Kcal mol.$^{-1}$

It is plausible that only one rotamer is present for compounds 138 since the NO_2 group may hydrogen bond to the NH group to stabilize this rotamer. There is no free NH on the -N moiety to stabilize the other rotamer.

3.7.0.0.0 Synthesis of N-{2-[4-(1-Methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl}-N'-homopiperidinyl(piperidinyl)-2-nitro-1,1-ethenediamines 156 and 158

The objective of this study was to investigate the effect which elaboration of the pyridinyl ring of 147 and 156 to a 1-methoxycarbonyl-1,2-dihydropyridinyl ring system had upon H_2-antagonist activity. The sodium borohydride reduction of the pyridinyl derivatives 147 and 156 in the presence of methyl chloroformate in methanol at -65°C yielded the respective 1,2-dihydropyridinyl analog 157 and 158 as illustrated by Scheme 7 and summarized in Table 16.

The 4-pyridinyl analog 156 was elaborated to the corresponding 4-(1-methoxycarbonyl-1,2-dihydropyridinyl derivative 158 to determine whether a similarly positioned 1,2-dihydropyridinyl ring system may be bioisosteric to a pyridinyl ring with respect to interaction with H_2-receptors. 1,2-Dihydropyridines are π-electron deficient ring systems which resemble pyridine. ^{1}H nmr studies indicated the π-electron densities at various positions in a N-carbonyl-1,2-dihydropyridinyl ring system are qualitatively similar to those of the analogous posi-


O2N
H
C
(CH2)n
CH2—S—CH2CH2—NH—C—N
N
O
Cl—C—OCH3
NaBH4
−65°C
O2N
H
C
(CH2)n
CH2—S—CH2CH2—NH—C—N
H
H
N
C=O
OCH3

147 (n=1)

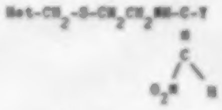
156 (n=2)

157 (n=1)

158 (n=2)

Scheme 7. Synthetic Routes Used for the Synthesis of N-{2-[4-(1-Methoxycarbonyl-1,2-dihydropyridinyl) methylthio] ethyl}-N'-homopiperidinyl(piperidinyl)-2-nitro-1,1-ethenediamines 157 and 158.

Table 16. Some Physical Data for N-[2-[4-(1-Methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl]-N'-[1-homopiperidinyl(piperidinyl)]-2-nitro-1,1-ethenediamines 157 and 158.



$$\text{Het-CH}_2\text{-S-CH}_2\text{CH}_2\text{NH-C-Y} \\ \| \\ \text{C} \\ \text{O}_2\text{N} \quad \text{H}$$

Compd	Het	Y	Yield,%	mp,°C	Formula	Mass[a] Calcd	Mass[a] Found
157	4-(1-methoxy-carbonyl-1,2-dihydropyridinyl	1-piperidinyl	58	121[b]	$C_{17}H_{26}N_4O_4S$	382.19	382.25
158	4-(1-methoxy-carbonyl-1,2-dihydropyridinyl)	1-homopiperidinyl	60	133[b]	$C_{18}H_{28}N_4O_4S$	396.2	396.45

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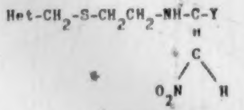
[a] Low resolution mass spectrum

[b] Dihydrogen hexachloroplatinate salt

Table 17. Infrared (ir) and Proton Magnetic Resonance (^{1}H nmr) Spectral Data for N-[2-[4-(1-Methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl]-N'-[homopiperidinyl(piperidinyl)]-2-nitro-1,1-ethenediamines 157 and 158.



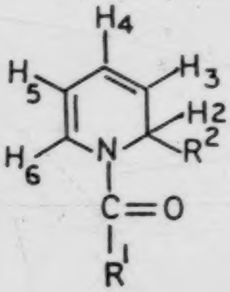
$$\text{Het-CH}_2\text{-S-CH}_2\text{CH}_2\text{-NH-}\underset{\underset{O_2N\quad H}{\overset{\parallel}{C}}}{\text{C}}\text{-Y}$$

Compd	Het	Y	ir, cm^{-1} (KBr) NO$_2$	ir, cm^{-1} (KBr) CO	ir, cm^{-1} (KBr) NH	^{1}H nmr, δ(CDCl$_3$)
157	4-(1-methoxy-carbonyl-1,2-dihydropyridinyl	1-piperidinyl	1500	1720	3350	1.4-2.13(complex m, 6H, piperidinyl H-3, H-4, H-5), 2.73(t, J=7Hz, 2H, CH$_2$CH$_2$N), 2.96-3.76(m, 6H, SCH$_2$CH$_2$N, piperidinyl H-2 and H-6), 3.68(s, 2H, dihydropyridinyl -CH$_2$-S), 3.8(s, 3H, OCH$_3$), 4.4(d, J$_{gem}$=3Hz, 2H, dihydropyridinyl H-2), 4.93-5.66(m, 2H, dihydropyridinyl H-3, H-5), 6.46(s, 1H, CHNO$_2$), 6.66-7.13(d, J$_{5,6}$=6Hz, 1H,

Table 17. (cont.)

						dihydropyridinyl H-6), 9.66(br s, 1H, NH, exchanges with deuterium oxide).
158	4-(1-methoxycarbonyl-1,2-dihydropyridinyl	1-homopiperidinyl	1500	1710	3350	1.4-2.1(complex m, 8H, homopiperidinyl H-3 to H-6), 2.69(t, J=7Hz, 2H, -$\underline{CH}_2$N), 3.03-3.66 (m, 6H, S$\underline{CH}_2$CH$_2$N, homopiperidinyl H-2 and H-7), 3.73(s, 2H, dihydropyridinyl -$\underline{CH}_2$-S), 3.85 (s, 3H, O$\underline{CH}_3$), 4.4(d, J_{gem}=3Hz, 2H, dihydropyridinyl H-2), 5.0-5.6(m, 2H, dihydropyridinyl H-3, H-5), 6.6(s, 1H, $\underline{CH}$NO$_2$), 6.66-7.0(d, $J_{5,6}$=6Hz, 1H, dihydropyridinyl H-6), 9.4(br s, 1H, NH, exchanges with deuterium oxide).

tions for a pyridine ring.[166,82,72,144,167] It is well documented that the chemical shift of a proton is dependent primarily on the electron density (degree of shielding) of the carbon atom to which it is attached.[168] The chemical shifts for protons present in a 1,2-dihydropyridinyl ring system appear in the following sequence of increasing δ values (decreasing electron density, decreased shielding): H-6 > H-4 > H-3 > H-5. The position of H-2 is variable and may appear at higher field than H-5 when the 2-substituent (R^2) is n-Bu or hydrogen, or between H-6 and H-4 when the 2-substituent is a phenyl substituent. These observations indicated that C-6, C-4 and C-2, when R^2 is a phenyl substituent, have the lowest π-electron density or charge distribution while the highest electron density is located at the C-3 and C-5 positions. Further precedent in support of the higher electron density at C-3 and C-5 of 1,2-dihydropyridines is evident since Freidel-Crafts alkylation and acylation, which are electrophilic reactions occured at the C-5 position.[169] The π-electron densities at the respective positions in 1,2-dihydropyridines are therefore qualitatively similar to the corresponding positions in pyridine as illustrated below.



The structure assigned to 158 was consistent with its ir, ^{1}H nmr

Table 18. Antagonism of Histamine Induced Guinea Pig Atria Chronotropic Response.

Compd	H_2-receptor antagonist activity pA_2(±SE)
142	<4.0
144	<4.0
150	3.61(0.113)
154	5.26(0.273)
156	4.53(0.151)
158	<4.0
Cimetidine	6.1[a]

[a] Literature value 154

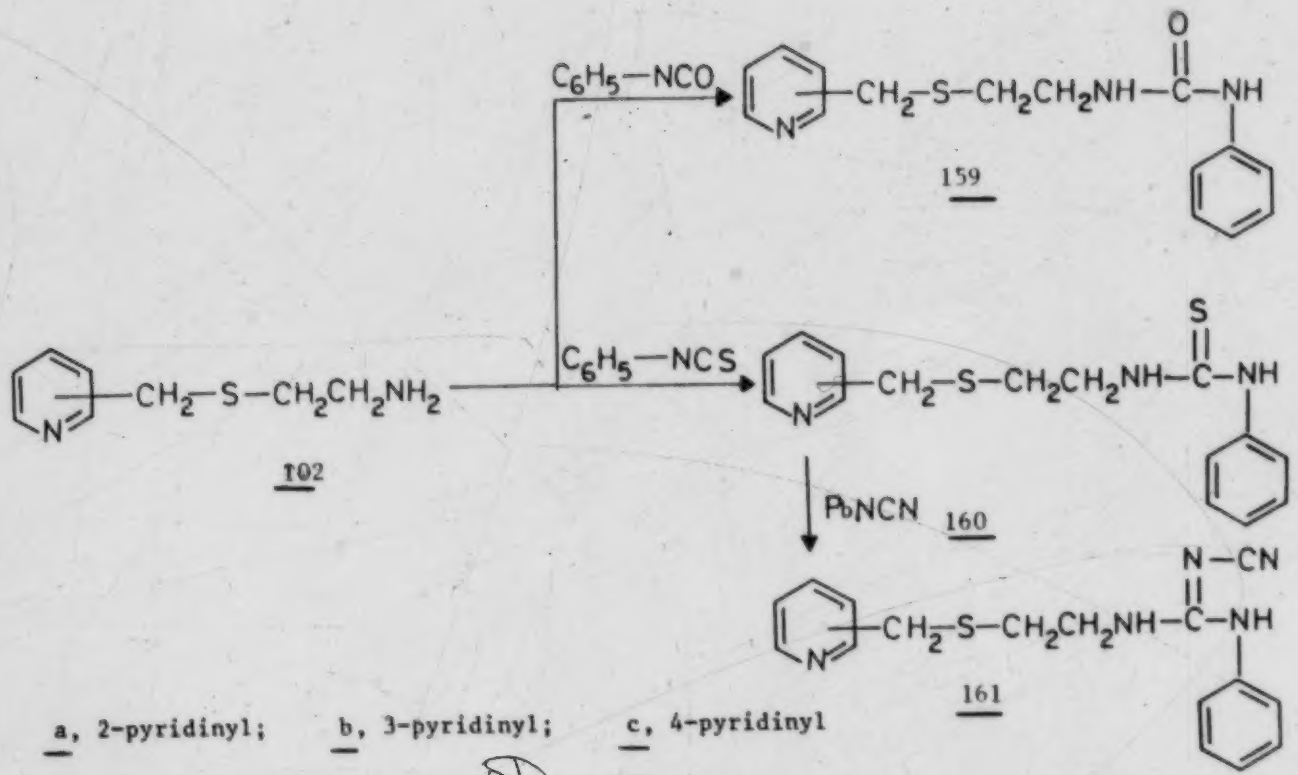
and mass spectrum. The ir spectrum showed the presence of a NO_2 absorption at 1500, a CO absorption at 1710 and an NH absorption at 3300 cm.$^{-1}$ The ^1H nmr spectrum (δ) for 158 in deutrochloroform exhibited a 8H broad multiplet at 1.4-2.1 assigned to the homopiperdinyl H-3 to H-6, a 2H triplet (J=7Hz) at 2.69 due to the $\underline{CH_2}N$, a 6H multiplet at 3.03-3.66 attributed to $S\underline{CH_2}CH_2N$ and homopiperidinyl H-2 and H-7, a 2H singlet at 3.73 for the dihydropyridinyl-$\underline{CH_2}$-S, a 3H singlet at 3.85 assigned to the $-O\underline{CH_3}$, a 2H doublet (J_{gem}=3Hz) at 4.4 due to H-2, a 2H multiplet at 5.0-5.6 attributed to the dihydropyridinyl H-3 and H-5, a 1H singlet at 6.6 assigned to $\underline{CH}NO_2$, a 1H doublet ($J_{5,6}$=7Hz) at 6.66-7.0 attributed to the dihydropyridinyl H-6 and a 1H broad singlet at 9.4 for the NH resonance which exchanged with deuterium oxide.

The mass spectrum was consistent with the assigned structure. The 4-(1-methoxycarbonyl-1,2-dihydropyridinyl) derivative 158 exhibited a pA_2 value of less than 4 in the guinea pig right atrium assay. This reduction in activity may be due to a lower π-electron density at C-4 for 156 relative to 158 since the size and shape of 156 and 158 are expected to be qualitatively similar. The observation that 156 was more active than 144 (See Table 18) suggests that affinity for the H_2-receptor is due, at least in part, to cooperative and dependent interactions of the molecular substructures, which include the heterocyclic ring and the 2-nitro-1,1-ethendiamine moiety, with the H_2-receptor.

3.8.0.0.0 Synthesis of N-Phenyl-N'-{2-[(2-(3-,4-)pyridinylmethylthio]ethyl}ureas 159, thioureas 160 and cyanoguanidines 161.

The urea, thiourea and cyanoguanidine analogs 159-161 were investigated to determine that effect which replacement of the terminal methyl substituent by a phenyl substituent had on H_2-receptor antagonist activity. The synthesis of the desired N-phenyl-N'-[2-(pyridinylmethylthio)ethyl]ureas 159 thioureas 160 and cyanoguanidines 161 is outlined in Scheme 8 and the results are summarized in Table 19. Thus, reaction of 102 with phenylisocyanate and phenylisothiocyanate gave the respective urea 159 and thiourea 160 derivatives. The cyanoguanidines 161 were prepared by the reaction of 160 with lead cyanamide in acetonitrile and dimethylformamide.

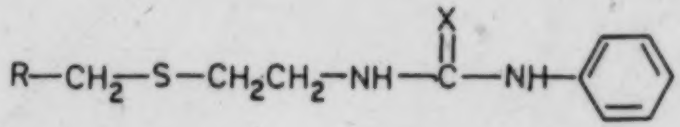
The ir and ^{1}H nmr data for compounds 159-161 are summarized in Table 20. Compounds 159-161 were prepared to investigate further the structural and chemical features of H_2-receptor antagonists. It is clear from the preliminary pharmacological test results obtained that replacement of the terminal methyl group in the side chain by a phenyl moiety reduced the H_2-receptor antagonistic activity dramatically. This indicates that a terminal alkyl or cycloalkylamino substituent is required for H_2-receptor antagonist activity.


C_6H_5-NCO
C_6H_5-NCS
PbNCN
102
159
160
161

a, 2-pyridinyl; b, 3-pyridinyl; c, 4-pyridinyl

Scheme 8. Synthetic Routes used for the Synthesis of N-Phenyl-N'-{2-[(2-(3-,4-)pyridinylmethylthio] ethyl]ethyl}ureas 159, thioureas 160 and cynaoguanidines 161.

Table 19. Some Physical Data for N-Phenyl-N'-{2-[2-(3-,4-)pyridinylmethylthio]ethyl}ureas 159, thioureas 160, and cyanoguanidines 161.

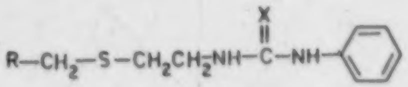


Compd	R	X	Reaction Time, h	Yield,%	Rf	mp, °C	Formula	Exact Mass Calcd.	Exact Mass Found
159a	2-pyridinyl	O	5-6	78	0.56	oil	$C_{15}H_{17}N_3OS$	287.1093	287.1094
159b	3-pyridinyl	O	5-6	71	0.58	oil	$C_{15}H_{17}N_3OS$	287.1093	287.1095
159c	4-pyridinyl	O	5-6	76	0.6	oil	$C_{15}H_{17}N_3OS$	287.1093	287.1101
160a	2-pyridinyl	S	8	80	0.7	oil	$C_{15}H_{17}N_3S_2$	303.0863	303.0845
160b	3-pyridinyl	S	8	73	0.72	oil	$C_{15}H_{17}N_3S_2$	303.0863	303.0845

Table 19. (cont.)

160c	4-pyridinyl	S	8	79	0.73	oil	$C_{15}H_{17}N_3S_2$	303.0864	303.0822
161a	2-pyridinyl	NCN	48	72	0.55	oil	$C_{16}H_{17}N_5S$	311.1205	311.1201
161b	3-pyridinyl	NCN	48	70	0.59	oil	$C_{16}H_{17}N_5S$	311.1205	311.1208
161c	4-pyridinyl	NCN	48	74	0.62	oil	$C_{16}H_{17}N_5S$	311.1205	311.1208

Table 20. Infrared (ir) and Proton Magnetic Resonance (^{1}H nmr) Spectral Data for N-Phenyl-N'-[2-[2-(3-,4-)pyridinylmethylthio]ethyl]ureas 159, thioureas 160 and cyanoguanidines 161.



			ir, cm^{-1} (KBr)		
Compd	R	X	>C=X	NH	^{1}H nmr, δ($CDCl_3$)
159a	2-pyridinyl	O	1650	3416	2.65(t, J=7Hz, 2H, -$\underline{CH_2}$S), 3.43(t, J=7Hz, 2H, S-$\underline{CH_2}$$CH_2$N), 3.85(s, 2H, pyr^a -$\underline{CH_2}$-S), 5.66-6.3(m, 1H, $CH_2\underline{NH}$, exchanges with deuterium oxide), 6.73-7.4(m, 8H, NH$C_6\underline{H_5}$, pyr^a H-3, H-5, $\underline{NH}C_6H_5$ which exchanges with deuterium oxide), 7.63(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-4), 8.53(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-6).
159b	3-pyridinyl	O	1650	3416	2.39(br s, 1H, $CH_2\underline{NH}$, exchanges with deuterium oxide), 2.83(t, J=7Hz, 2H, -$\underline{CH_2}$S), 3.79(s, 2H, pyr^a

Table 20. (cont.)

					$-\underline{CH}_2$-S), 3.84(t, J=7Hz, 2H, $S\underline{CH}_2CH_2N$), 6.59(br s, 1H, $\underline{NH}C_6H_5$, exchanges with deuterium oxide), 7.16-8.0(m, 7H, $NHC_6\underline{H}_5$, pyr^a H-4, H-5), 8.33-8.8(m, 2H, pyr^a H-2, H-6).
159c	4-pyridinyl	O	1650	3384	2.73(t, J=7Hz, 2H, $-\underline{CH}_2N$), 3.75(s, 2H, pyr^a $-\underline{CH}_2$-S), 3.93(t, J=7Hz, 2H, $S-\underline{CH}_2CH_2-N$), 6.33-6.76(br s, 1H, $CH_2\underline{NH}$, exchanges with deuterium oxide), 7.0-7.6(m, 8H, $NHC_6\underline{H}_5$, pyr^a H-3, H-5, $\underline{NH}C_6H_5$, exchanges with deuterium oxide), 8.58(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyr^a H-2, H-6).
160a	2-pyridinyl	S	1090	3320	2.65(t, J=7Hz, 2H, $-\underline{CH}_2N$), 3.43(t, J=7Hz, 2H, $S\underline{CH}_2CH_2N$), 3.05(s, 2H, pyr^a $-\underline{CH}_2$-S), 5.66-6.3 (br s, 1H, $CH_2\underline{NH}$, exchanges with deuterium oxide), 6.73-7.4(m, 8H, $NHC_6\underline{H}_5$, pyr^a H-3, H-5, $\underline{NH}C_6H_5$, exchanges with deuterium oxide), 7.63(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-4), 8.53(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-6).

Table 20. (cont.)

160b	3-pyridinyl	S	1090	3320	2.39(br s, 1H, $CH_2\underline{NH}$, exchanges with deuterium oxide), 2.83(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.79(s, 2H, pyr^a $-\underline{CH_2}-S$), 3.84(t, J=7Hz, 2H, $S\underline{CH_2}CH_2N$), 6.59(br s, 1H, $\underline{NH}C_6H_5$, exchanges with deuterium oxide), 7.16-8.0(m, 7H, $NHC_6\underline{H_5}$, pyr^a H-4, H-5), 8.33-8.8(m, 2H, pyr^a H-2, H-6).
160c	4-pyridinyl	S	1090	3320	2.71(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.71(s, 2H, pyr^a $-\underline{CH_2}-S$), 3.91(t, J=7Hz, 2H, $S\underline{CH_2}CH_2N$), 6.33-6.76(m, 1H, $CH_2\underline{NH}$, exchanges with deuterium oxide), 7.0-7.6(m, 8H, $NHC_6\underline{H_5}$, pyr^a H-3, H-5, and $\underline{NH}C_6H_5$, exchanges with deuterium oxide), 8.50(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^a H-2, H-6).
161a	2-pyridinyl	NCN	2168	3350	2.65(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.43(t, J=7Hz, 2H, $S\underline{CH_2}CH_2N$), 3.85(s, 2H, pyr^a $-\underline{CH_2}-S$), 6.0(br s, 1H, $CH_2\underline{NH}$, exchanges with deuterium oxide), 7.0-7.4(m, 8H, $NHC_6\underline{H_5}$, pyr^a H-3, H-5, $\underline{NH}C_6H_5$, exchanges with deuterium oxide), 7.63(d, $J_{3,4}=8Hz$

Table 20. (cont.)

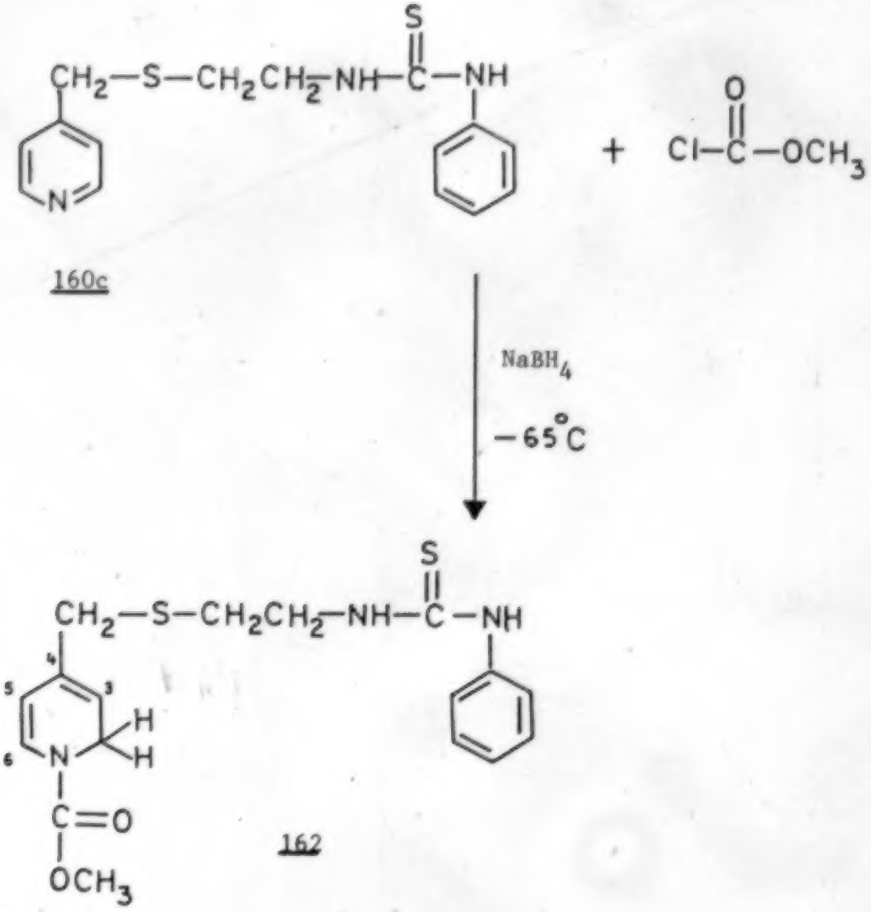
					of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr[a] H-4), 8.53(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr[a] H-6).
161b	3-pyridinyl	NCN	2168	3350	2.39(br s, 1H, CH_2NH, exchanges with deuterium oxide), 2.83(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.79(s, 2H, pyr[a] $-\underline{CH_2}-S$), 3.84(t, J=7Hz, 2H, $S\underline{CH_2}CH_2N$), 6.59(br s, 1H, $\underline{NH}C_6H_5$, exchanges with deuterium oxide), 7.16-8.0(m, 7H, $NHC_6\underline{H_5}$, pyr[a] H-4, H-5), 8.6-8.8(m, 2H, pyr[a] H-2, H-6).
161c	4-pyridinyl	NCN	2168	3350	2.71(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.7(s, 2H, pyr[a] $-\underline{CH_2}-S$), 3.89(t, J=7Hz, 2H, $S\underline{CH_2}CH_2N$), 6.33-6.76(m, 1H, $CH_2\underline{NH}$, exchanges with deuterium oxide), 7.0-7.6 (m, 8H, $NHC_6\underline{H_5}$, pyr[a] H-3 and H-5, $\underline{NH}C_6H_5$, exchanges with deuterium oxide), 8.50(d, $J_{2,3}$=$J_{5,6}$=6Hz, 2H, pyr[a] H-2, H-6).

---

[a] pyr denotes pyridine

3.9.0.0.0 Synthesis of N-Phenyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl}thiourea 162.

Sodium borohydride reduction of the pyridine derivative 160c in the presence of methyl chloroformate in methanol at -65°C yielded the respective 1,2-dihydropyridinyl analog 162 in 70% yield as shown in Scheme 9.

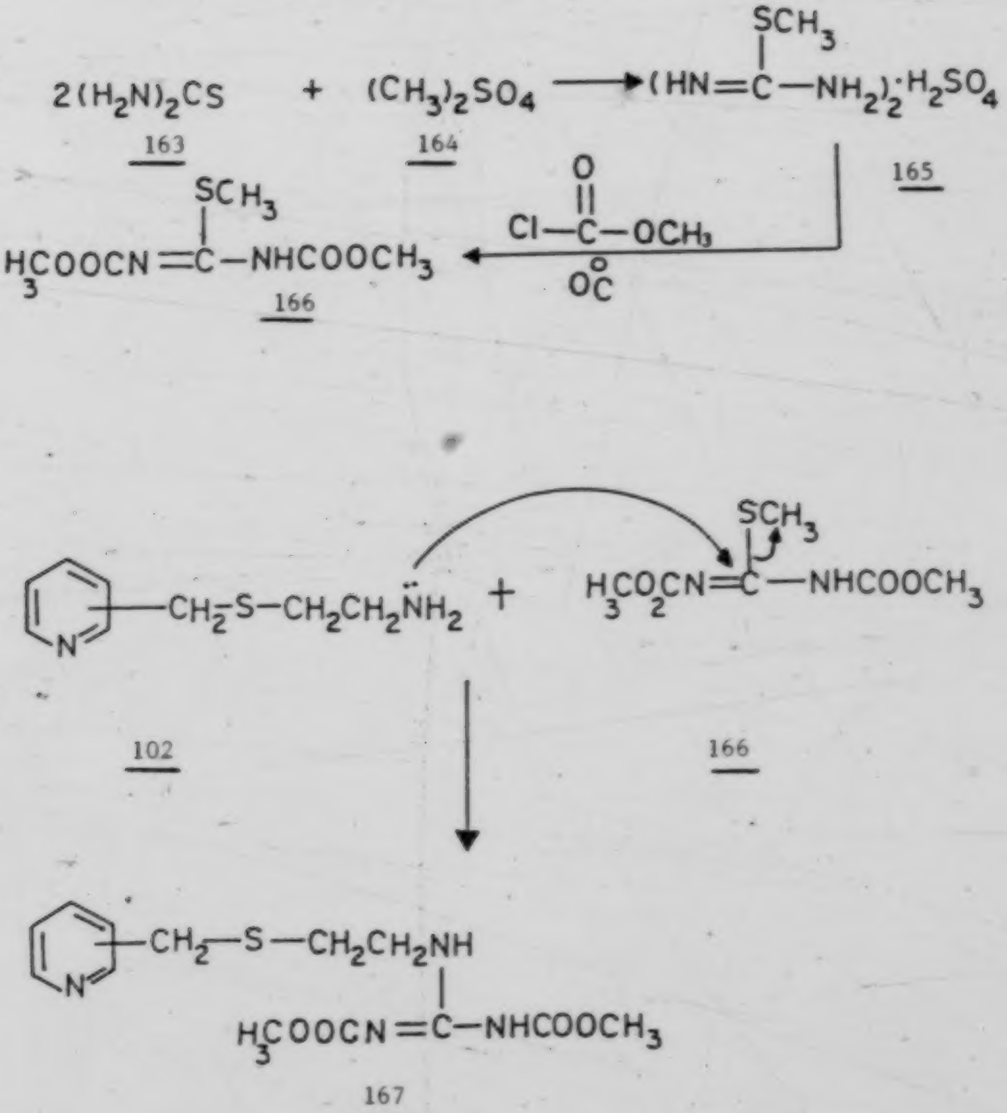


Scheme 9. Synthetic Route used for the Synthesis of N-Phenyl-N'-{2-[4-(1-methoxycarbonyl-1,2 dihydropyridinyl)methylthio] ethyl}thiourea 162.

The structure assigned to 162 was consistent with its ir, ^1H nmr, and high resolution mass spectrometric data. The ir spectrum showed an NH absorption at 3320, a C=S absorption at 1090 and a CO group absorption at 1710 cm^{-1}. The ^1H nmr of 162 in deutrochloroform (δ) exhibited a 2H triplet (J=7Hz) at 2.7 assigned to the CH_2N, a 2H singlet at 3.12 due to the dihydropyridinyl $-\underline{CH_2}-S$, a 3H singlet at 3.75 attributed to the $O-CH_3$, a 2H triplet (J=7Hz) at 3.9 assigned to $S\underline{CH_2}CH_2N$, a 2H doublet (J_{gem}=3Hz) at 4.37 due to the dihydropyridinyl H-2, a 1H multiplet at 5.1 due to H-5, a 1H multiplet at 5.4 attributed to H-3, a 1H broad singlet at 6.5 assigned to $CH_2\underline{NH}$, which exchanges with deuterium oxide, a 1H doublet ($J_{5,6}$=8Hz) at 6.75 assigned to the dihydropyridinyl H-6, a 5H multiplet at 7.17-7.62 due to C_6H_5 and a 1H broad singlet at 8.07 attributed to the $\underline{NH}C_6H_5$ which exchanges with deuterium oxide. The mass spectrum exhibited the following; Exact Mass Calcd. for $C_{17}H_{21}N_3O_2S_2^{32}$:363.1076; Found:363.1078.

4.0.0.0.0 Synthesis of N,N"-Dimethoxycarbonyl-N'-{2-[2-(3-,4-)-pyridinylmethylthio]ethyl}guanidines 167

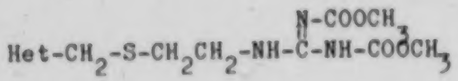
The goal of this study was to investigate the effect which replacement of the cyano and terminal methyl substituents of the cyanoguanidine moiety by methoxycarbonyl substituents would have on H_2-receptor antagonist activity. These changes, especially replacement of the terminal methyl substituent, were expected to have a pronounced effect upon H_2-receptor binding. The synthesis of the target N,N"-dimethoxycarbonyl-N'-[2-(pyridinylmethylthio)ethyl]guanidines 167 is outlined in Scheme 10 and the results are summarized in Table 21.


2(H2N)2CS
163
(CH3)2SO4
164
(HN=C(SCH3)—NH2)2·H2SO4
165
Cl—C(=O)—OCH3
0°C
H3COOCN=C(SCH3)—NHCOOCH3
166
CH2—S—CH2CH2NH2
102
H3CO2CN=C(SCH3)—NHCOOCH3
166
CH2—S—CH2CH2NH
H3COOCN=C—NHCOOCH3
167

a, 2-pyridinyl: **b,** 3-pyridinyl; **c,** 4-pyridinyl

Scheme 10. Synthetic Routes Used for the Synthesis of N,N"-Dimethoxycarbonyl-N'-{2-[2-(3-,4-)-pyridinylmethylthio]ethyl} guanidines 167.

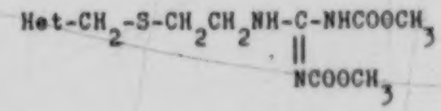
Table 21. Some Physical Data for N,N"-Dimethoxycarbonyl-N'-{2-[2-(3-,4-)pyridinylmethylthio]ethyl} guanidines 167.



$$\text{Het-CH}_2\text{-S-CH}_2\text{CH}_2\text{-NH-}\overset{\text{N-COOCH}_3}{\overset{\|}{\text{C}}}\text{-NH-COOCH}_3$$

Compd	Het	Rf	Yield,%	Reaction Time,h	mp,°C	Formula	Exact Mass Calcd	Exact Mass Found
167a	2-pyridinyl	0.7	83	3	oil	$C_{13}H_{18}N_4O_4S$	326.1049	326.1049
167b	3-pyridinyl	0.65	79	3	oil	$C_{13}H_{18}N_4O_4S$	326.1049	326.1038
167c	4-pyridinyl	0.68	81	3	oil	$C_{13}H_{18}N_4O_4S$	326.1049	326.1041

Table 22. Infrared (ir) and Proton Magnetic Resonance (^{1}H nmr) Spectral Data for N,N"-Dimethoxycarbonyl-N'-[2-[2-(3-,4-)pyridinylmethylthio]ethyl]guanidines 167



$$\text{Het-CH}_2\text{-S-CH}_2\text{CH}_2\text{NH-}\underset{\underset{\text{NCOOCH}_3}{\|}}{\text{C}}\text{-NHCOOCH}_3$$

Compd	Het	ir, cm^{-1} (KBr) O=C	NH	^{1}H nmr, δ(CDCl$_3$)
167a	2-pyridinyl	1730	3320	2.74(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.62(t, J=7Hz, 2H, $S\underline{CH_2}CH_2N$), 3.72 and 3.8(two s, 3H each, $NHCO_2\underline{CH_3}$ and $NCOO\underline{CH_3}$), 3.88(s, 2H, pyr[a] $-\underline{CH_2}-S$), 7.2(d, $J_{4,5}$=8Hz of d, $J_{5,6}$=5Hz of d, $J_{3,5}$=1.5Hz, 1H, pyr[a] H-5), 7.42(d, $J_{4,5}$=8Hz, 1H, pyr[a] H-3), 7.7(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr[a] H-4), 8.54(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr[a] H-6), 8.66(br s, 1H, $CH_2\underline{NH}$, exchanges with deuterium oxide), 9.8(br s, 1H, $\underline{NH}COOMe$, exchanges with deuterium oxide).
a67b	3-pyridinyl	1730	3320	2.66(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.46(t, J=7Hz, 2H, $S\underline{CH_2}CH_2N$), 3.72(br s, 6H, $NCOO\underline{CH_3}$ and $NHCOO\underline{CH_3}$), 3.76(s, 2H, pyr[a]

Table 22. (cont.)

				-$\underline{CH}_2$-S), 6.6-7.4(br s, 2H, two NH protons, exchange with deuterium oxide), 7.3(d, $J_{4,5}$=8Hz of d, $J_{5,6}$=6Hz, 1H, pyr[a] H-5), 7.2(d, $J_{4,5}$=8Hz, 1H, pyr[a] H-4), 8.46-8.66(m, 2H, pyr[a] H-2, H-6).
167c	4-pyridinyl	1730	3320	2.64(t, J=7Hz, 2H, -$\underline{CH}_2$N), 3.64(t, J=7Hz, 2H, S$\underline{CH}_2$CH$_2$N), 3.74 and 3.78(two s, 3H each NHCOO$\underline{CH}_3$ and NCOO$\underline{CH}_3$), 3.84(s, 2H, pyr[a] -$\underline{CH}_2$-S), 7.32(d, $J_{2,3}$=$J_{5,6}$=6Hz, 2H, pyr[a] H-3, H-5), 8.5-8.7(m, 3H, CH$_2\underline{NH}$, exchanges with deuterium oxide, pyr[a] H-2, H-6), 11.7(br s, 1H, $\underline{NH}$COOCH$_3$, exchanges with deuterium oxide).

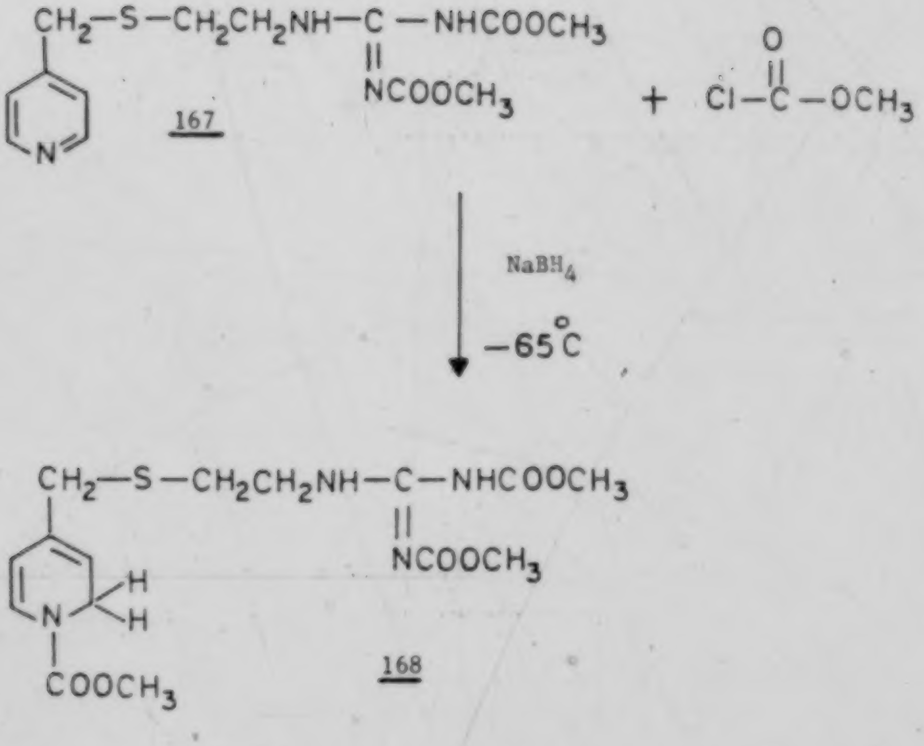
---

[a] pyr denotes pyridine

Thus, reaction of thiourea 163 with dimethylsulfate afforded S-methylisothiourea sulfate 165 in high yield (72%). Reaction of 165 with methyl chloroformate at 0°C afforded N,N'-dimethoxycarbonyl-S-methylisothiourea 166 in 67.5% chemical yield. The N,N"-dimethoxycarbonyl-N'-[2-(pyridinylmethylthio)ethyl]guanidines 167 were obtained via reaction of the amine 102 with 166 using p-toluenesulfonic acid as catalyst in methanol as solvent. The ir and ^{1}H nmr data for compounds 167 are summarized in Table 22. The N,N"-dimethoxycarbonyl compounds 167 were prepared to determine what effect replacement of the cyano substituent of the cyanoguanidine moiety by an electron attracting N-carbomethoxy substituent which resembles the CN group and the terminal methyl group by a methoxycarbonyl substituent has upon H_2-receptor antagonistic activity. Preliminary pharmacological screening indicated these replacements reduced the potency of the H_2-antagonists. Compounds 159a, 160c, 161a, 161c, and 167a demonstrated no significant antagonism to histamine at a 10^{-4}M concentration. The structure assigned to 167a was consistent with the ir, ^{1}H nmr and high resolution mass spectrometric data obtained.

4.1.0.0.0 Synthesis of N,N"-Dimethoxycarbonyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinylmethylthio]ethyl}guanidine 168.

The sodium borohydride reduction of the pyridinyl derivative 167c in the presence of methyl chloroformate in methanol at -65°C yielded the respective 1,2-dihydropyridinyl analog 168 as illustrated in Scheme 11.



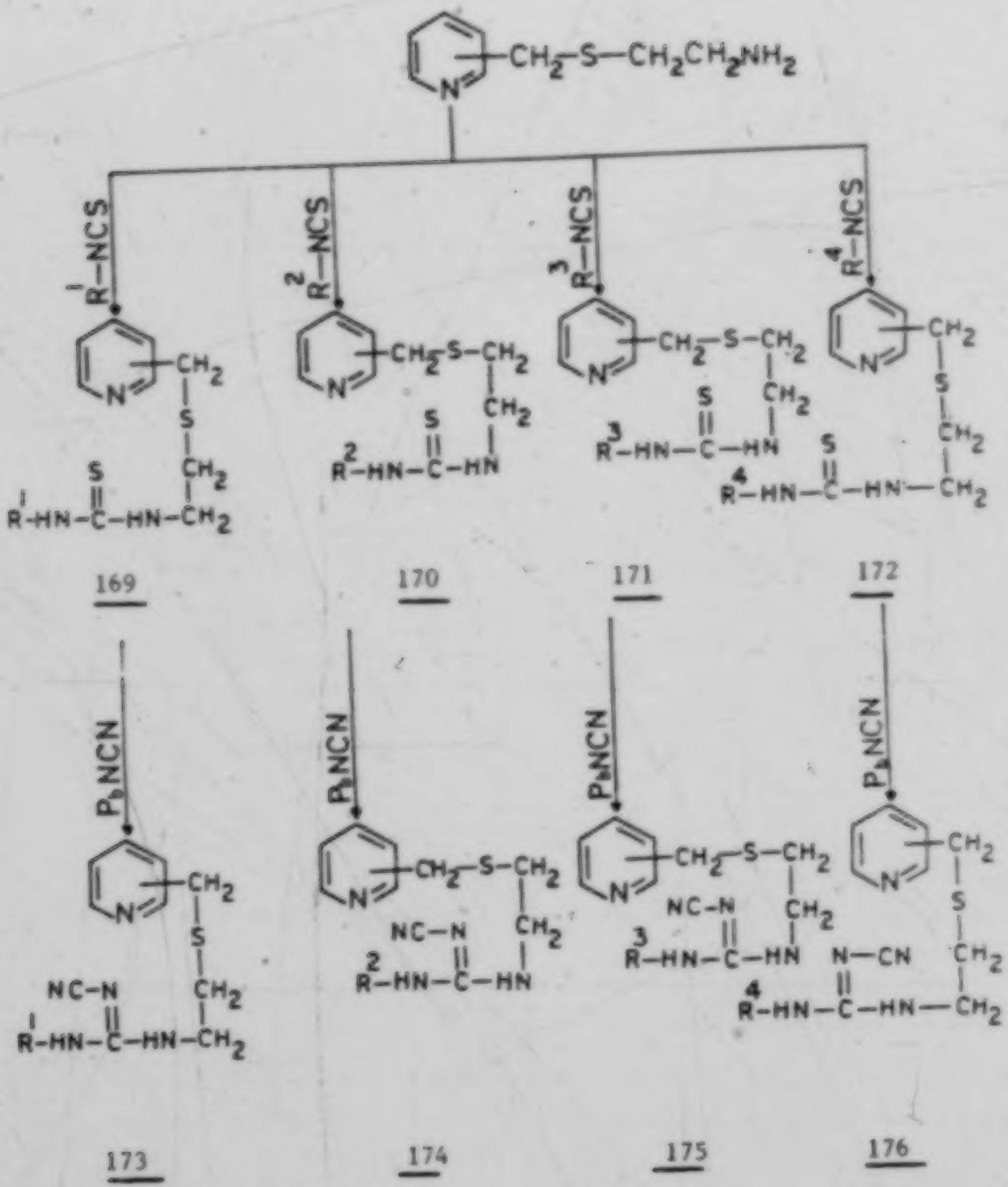
$CH_2-S-CH_2CH_2NH-C(=NCOOCH_3)-NHCOOCH_3$
167
$+ Cl-C(=O)-OCH_3$
$NaBH_4$
−65°C
$CH_2-S-CH_2CH_2NH-C(=NCOOCH_3)-NHCOOCH_3$
H
H
N
$COOCH_3$
168

Scheme 11. Synthetic Route Used for the Synthesis of N,N"-Dimethoxycarbonyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinylmethylthio]ethyl}guanidine 168.

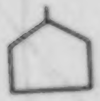
The structure assigned to 168 was consistent with its ir, ^{1}H nmr and high resolution mass spectrometric data. The ir spectrum showed an NH absorption at 3320 and a CO group absorption at 1720 cm^{-1}. The ^{1}H nmr spectrum of 168 in deuterochloroform (δ) exhibited a 2H triplet (J=7Hz) at 2.66 assigned to the -$\underline{CH_2}$N, a 2H singlet at 3.13 due to the 1,2-dihydropyridinyl -$\underline{CH_2}$-S, a 2H triplet (J=7Hz) at 3.63 attributed to the S$\underline{CH_2}$CH$_2$, two 3H singlets at 3.73 and 3.83 due to the NHCOO$\underline{CH_3}$ and NCOO$\underline{CH_3}$ resonances, a 2H doublet (J_{gem}=3Hz) at 4.4 attributed to the dihydropyridinyl H-2, a 2H multiplet at 5.0-5.66 assigned to the dihydropyridinyl H-3, H-5, a 1H doublet ($J_{5,6}$=6Hz) at 6.83 due to the dihydropyridinyl H-6 and a 2H multiplet at 8.33-9.0 attributed to the two NH protons. Exact Mass Calcd. for $C_{15}H_{22}N_4O_6S^{32}$: 386.1260; found, 386.1251.

4.2.0.0.0 Synthesis of N-Alkyl(cycloalkyl)-N'-[2-(pyridinylmethylthio)ethyl]thioureas 169-172 and cyanoguanidines 173-176.

The pyridinyl thiourea and cyanoguanidine analogs 169-176 were prepared to investigate the effect which replacement of the terminal methyl substituent of the side chain by higher alkyl and cycloalkyl moieties has upon H$_2$-receptor antagonist activity. The synthetic procedures used for the synthesis of the desired N-alkyl(cycloalkyl)-N'-[2-(pyridinylmethylthio)ethyl]thioureas 169-172 and cyanoguanidines 173-176 is outlined in Scheme 12 and the products obtained are


CH2-S-CH2CH2NH2
R1-NCS
R2-NCS
R3-NCS
R4-NCS
169
170
171
172
PhNCN
PhNCN
PhNCN
PhNCN
173
174
175
176

$R^1 =$



$R^2 = CH_2CH_2CH_2CH_3$

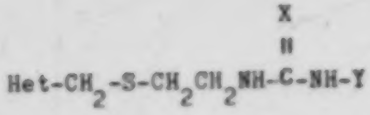
$R^3 = CH_2CH_2CH_3$

$R^4 = CH_2CH_3$

a, 2-pyridinyl; b, 3-pyridinyl; c, 4-pyridinyl

Scheme 12. Synthesis of N-Alkyl(cycloalkyl)-N'-[2-(pyridinylmethylthio)ethyl]thioureas 169-172 and cyanoguanidines 173-176.

Table 23. Some Physical Data for N-Alkyl(cycloalkyl)-N'-[2-(pyridinylmethylthio)ethyl]thioureas $^{169-172}$ and cyanoguanidines 173-176.



$$\text{Het-CH}_2\text{-S-CH}_2\text{CH}_2\text{NH-}\overset{\overset{\displaystyle X}{\|}}{\text{C}}\text{-NH-Y}$$

				Reaction					Exact Mass	
Compd	Het	X	Y	Time(h)	Yield,%	Rf	mp,°C	Formula	Calcd	Found
169a	2-pyridinyl	S	cyclopentyl	18	81	0.58	oil	$C_{14}H_{21}N_3S_2$	295.1177	295.1184
169b	3-pyridinyl	S	cyclopentyl	18	79	0.5	oil	$C_{14}H_{21}N_3S_2$	295.1177	295.1187
169c	4-pyridinyl	S	cyclopentyl	18	84	0.54	oil	$C_{14}H_{21}N_3S_2$	295.1177	295.1187
170a	2-pyridinyl	S	n-butyl	14	75	0.6	oil	$C_{13}H_{21}N_3S_2$	283.1177	283.1183

Table 23 (cont.)

170b	3-pyridinyl	S	n-butyl	14	73	0.6	oil	$C_{13}H_{21}N_3S_2$	283.1177	283.1188
170c	4-pyridinyl	S	n-butyl	14	76	0.6	oil	$C_{13}H_{21}N_3S_2$	283.1177	283.1165
171a	2-pyridinyl	S	n-propyl	14	70	0.62	oil	$C_{12}H_{19}N_3S_2$	269.1020	269.1020
171b	3-pyridinyl	S	n-propyl	14	70	0.6	oil	$C_{12}H_{19}N_3S_2$	269.1020	269.1019
171c	4-pyridinyl	S	n-propyl	14	74	0.6	oil	$C_{12}H_{19}N_3S_2$	269.1020	269.1019
172a	2-pyridinyl	S	ethyl	10	65	0.55	oil	$C_{11}H_{17}N_3S_2$	255.0864	255.0868
172b	3-pyridinyl	S	ethyl	10	62	0.6	oil	$C_{11}H_{17}N_3S_2$	255.0864	255.0864
172c	4-pyridinyl	S	ethyl	10	69	0.58	oil	$C_{11}H_{17}N_3S_2$	255.0864	255.0872

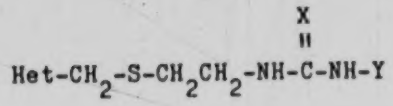
Table 23. (cont.)

173a	2-pyridinyl	NCN	cyclopentyl	48	70	0.6	oil	$C_{15}H_{21}N_5S$	303.1518	303.1508
173b	3-pyridinyl	NCN	cyclopentyl	48	69	0.65	oil	$C_{15}N_{21}N_5S$	303.1518	303.1514
173c	4-pyridinyl	NCN	cyclopentyl	48	72	0.6	oil	$C_{15}H_{21}N_5S$	303.1518	303.1520
174a	2-pyridinyl	NCN	n-butyl	48	72	0.6	oil	$C_{14}H_{21}N_5S$	291.1518	291.1518
174b	3-pyridinyl	NCN	n-butyl	48	70	0.6	oil	$C_{14}H_{21}N_5S$	291.1518	291.1515
174c	4-pyridinyl	NCN	n-butyl	48	73	0.6	oil	$C_{14}H_{21}N_5S$	291.1518	291.1512
175a	2-pyridinyl	NCN	n-propyl	48	74	0.58	oil	$C_{13}H_{19}N_5S$	277.1361	277.1360
175b	3-pyridinyl	NCN	n-propyl	48	70	0.6	oil	$C_{13}H_{19}N_5S$	277.1361	277.1359

Table 23. (cont.)

175c	4-pyridinyl	NCN	n-propyl	48	74	0.6	oil	$C_{13}H_{19}N_5S$	277.1361	277.1359
176a	2-pyridinyl	NCN	ethyl	48	68	0.6	oil	$C_{12}H_{17}N_5S$	263.1205	263.1202
176b	3-pyridinyl	NCN	ethyl	48	65	0.6	oil	$C_{12}H_{17}N_5S$	263.1205	263.1208
176c	4-pyridinyl	NCN	ethyl	48	70	0.6	oil	$C_{12}H_{17}N_5S$	263.1205	263.1205

Table 24. Infrared (ir) and Proton Magnetic Resonance (^{1}H nmr) Spectral Data for N-Alkyl(cycloalkyl)-N'-[2-(3-,4-)pyridinylmethylthio)ethyl]thioureas 169-172 and cyanoguanidines 173-176.



$$\text{Het-CH}_2\text{-S-CH}_2\text{CH}_2\text{-NH-}\overset{\overset{\displaystyle X}{\|}}{\text{C}}\text{-NH-Y}$$

Compd	Het	X	Y	ir, cm^{-1}(KBr)		^{1}H nmr, δ(CDCl$_3$)
				C=X	NH	
169a	2-pyridinyl	S	cyclopentyl	1090	3256	1.4-2.3(m, 8H, cyclopentyl H-2 to H-5), 2.7(t, J=7Hz, 2H, -CH$_2$N), 3.7(t, 7=7Hz, 2H, SCH$_2$CH$_2$), 3.9(s, 2H, pyr^a-CH$_2$-S), 4.25(m, 1H, cyclopentyl H-1), 5.9-7.03(m, 2H, two NH protons, exchange with deuterium oxide), 7.0-7.46(m, 2H, pyr^a H-3, H-5), 7.66(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-4), 8.46(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-6).

Table 24. (cont.)

169b	3-pyridinyl	S	cyclopentyl	1090	3256	1.4-2.26(m, 8H, cyclopentyl H-2 to H-5), 2.73(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.73(t, J=7Hz, 2H, S$\underline{CH_2}$CH$_2$), 3.76 (s, 2H, pyr^a -$\underline{CH_2}$-S), 4.1(m, 1H, cyclopentyl H-1), 6.2-6.73(m, 2H, two NH protons, exchange with deuterium oxide), 7.13-7.46(m, 1H, pyr^a H-5), 7.6-7.9(m, 1H, pyr^a H-4), 8.43-8.7(m, 2H, pyr^a H-2, H-6).
169c	4-pyridinyl	S	cyclopentyl	1090	3256	1.13-2.2(m, 8H, cyclopentyl H-2 to H-5), 2.63(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.33-4.33(m, 5H, pyr^a -$\underline{CH_2}$-S, S$\underline{CH_2}$CH$_2$N, and cyclopentyl H-1), 5.9-6.56(m, 2H, two NH protons, exchange with deuterium oxide), 7.23(d, $J_{2,3}=J_{5,6}=6$Hz, 2H, pyr^a H-3, H-5), 8.5(d, $J_{2,3}=J_{5,6}=6$Hz, 2H, pyr^a H-2, H-6).

Table 24. (cont.)

170a	2-pyridinyl	S	n-butyl	1090	3256	0.94(t, J=7Hz, 3H, CH_3), 1.14-1.8(m, 4H, $NH\text{-}CH_2\underline{CH_2}\underline{CH_2}\text{-}$), 2.76(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.3-3.6(m, 2H, $NH\underline{CH_2}CH_2\text{-}$) 3.8(t, J=7Hz, 2H, $S\text{-}\underline{CH_2}CH_2$), 3.9(s, 2H, pyr^a $-\underline{CH_2}\text{-}S$), 6.5 and 7.02(br s, 1H each, $\underline{NH}$-Bu and $S\text{-}CH_2CH_2\underline{NH}\text{-}$, exchange with deuterium oxide), 7.16-7.5(m, 2H, pyr^a H-3, H-5), 7.74(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-4), 8.54(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-6).
170b	3-pyridinyl	S	n-butyl	1090	3256	1.06(t, J=7Hz, 3H, $-CH_3$), 1.2-2(m, 4H, $NH\text{-}CH_2\underline{CH_2}\underline{CH_2}$), 2.8(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.2-3.63(m, 2H, $NH\underline{CH_2}CH_2\text{-}$), 3.63-4.1(m, 4H, pyr^a $-\underline{CH_2}\text{-}S$ and $S\text{-}\underline{CH_2}CH_2$), 6.1-6.86(m, 2H, two NH protons, exchange with deuterium oxide),

Table 24. (cont.)

						7.2-7.56(m, 1H, pyr^a H-5), 7.66-8.0(m, 1H, pyr^a H-4), 8.5-8.83(m, 2H, pyr^a H-2, H-6).
170c	4-pyridinyl	S	n-butyl	1090	3256	0.9(t, J=7Hz, 3H, $-CH_3$), 1.06-1.8(m, 4H, $NH-CH_2\underline{CH_2CH_2}$), 2.66(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.1-3.53(m, 2H, $NH\underline{CH_2}CH_2$), 3.7(s, 2H, pyr^a $-\underline{CH_2}-S$), 3.76(t, J=7Hz, 2H, $S\underline{CH_2}CH_2$), 6.33-7.0(m, 2H, two NH protons, exchange with deuterium oxide), 7.26(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^a H-3, H-5), 8.5(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^a H-2, H-6.
171a	2-pyridinyl	S	n-propyl	1090	3256	0.9(t, J=7Hz, 3H, $CH_2\underline{CH_3}$), 1.23-1.9(m, 2H, $CH_2\underline{CH_2}CH_3$), 2.76(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.43

Table 24. (cont.)

						(complex m, 2H, $NH\underline{CH_2}CH_2CH_3$, collapses to a triplet after deuterium oxide exchange), 3.76(t, J=7Hz 2H, $S\underline{CH_2}CH_2$), 3.9(s, 2H, pyr^a -$\underline{CH_2}$-S), 6.36 and 6.93(br s, 1H each, $\underline{NH}$-propyl and S-$CH_2CH_2\underline{NH}$-, exchange with deuterium oxide, 7.2-7.53(m, 2H, pyr^a H-3, H-5), 7.76(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-4), 8.56(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-6).
171b	3-pyridinyl	S	n-propyl	1090	3256	0.9(t, J=7Hz, 3H, -$CH_2\underline{CH_3}$), 1.23-1.83(m, 2H, $CH_2\underline{CH_2}CH_3$), 2.66(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.3 (m, 2H, $NH\underline{CH_2}CH_2CH_3$, collapses to a triplet after deuterium oxide exchange), 3.7(t, J=7Hz, 2H, $S\underline{CH_2}CH_2$), 3.73(s, 2H, pyr^a -$\underline{CH_2}$-S), 6.33-6.8(m, 2H, two NH protons, exchange with deuterium oxide), 7.1-7.43(m, 1H, pyr^a H-5),

Table 24. (cont.)

						7.56-7.86(m, 1H, pyr^{a} H-4), 8.4-8.73(m, 2H, pyr^{a} H-2, H-6).
171c	4-pyridinyl	S	n-propyl	1090	3256	0.93(t, J=7Hz, 3H, $-CH_2\underline{CH_3}$), 1.2-1.86(m, 2H, $CH_2\underline{CH_2}CH_3$), 2.7(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.3(m, 2H, $NH\underline{CH_2}CH_2CH_3$, collapses to a triplet after deuterium oxide exchange), 3.7(t, J=7Hz, 2H, $S\underline{CH_2}CH_2$), 3.73(s, 2H, pyr^{a} $-\underline{CH_2}-S$) 6.0-6.5(m, 2H, two NH protons, exchange with deuterium oxide), 7.33(d, $J_{2,3}=J_{5,6}=6$Hz, 2H, pyr^{a} H-3, H-5), 8.56(d, $J_{2,3}=J_{5,6}=6$Hz, 2H, pyr^{a} H-2, H-6).
172a	2-pyridinyl	S	ethyl	1090	3256	1.3(t, J=7Hz, 3H, $CH_2\underline{CH_3}$), 2.03(br s, 1H,

Table 24. (cont.)

						$\underline{NH}$-Et, exchanges with deuterium oxide), 2.83(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.4-3.76(m, 2H, NH$\underline{CH_2}$CH$_3$, collapses to a quartet after deuterium oxide exchange), 3.76(t, J=7Hz, 2H, S$\underline{CH_2}$CH$_2$), 3.96(s, 2H, pyr^a -$\underline{CH_2}$-S), 6.46(br s, 1H, CH$_2\underline{NH}$CSNH, exchanges with deuterium oxide), 7.16-7.5(m, 2H, pyr^a H-3, H-5), 7.76(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-4), 8.63(d, $J_{5,6}$=5Hz of d $J_{4,6}$=2Hz, 1H, pyr^a H-6).
$\underline{172b}$	3-pyridinyl	S	ethyl	1090	3256	1.2(t, J=7Hz, 3H, CH$_2\underline{CH_3}$), 2.7(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.2-3.66(m, 2H, NH$\underline{CH_2}$CH$_3$, collapses to a quartet after deuterium oxide exchange), 3.76(t, J=7Hz, 2H, S$\underline{CH_2}$CH$_2$), 3.8(s, 2H, pyr^a -$\underline{CH_2}$-S), 6.13-6.73(m, 2H, two NH protons,

Table 24. (cont.)

						exchange with deuterium oxide), 7.16-7.5(m, 1H, pyr^a H-5), 7.56-7.93(m, 1H, pyr^a H-4), 8.4-8.76(m, 2H, pyr^a H-2, H-6).
172c	4-pyridinyl	S	ethyl	1090	3256	1.2(t, J=7Hz, 3H, $CH_2\underline{CH_3}$), 2.66(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.1-3.56(m, 2H, $NH\underline{CH_2}CH_3$, collapses to a quartet after deuterium oxide exchange), 3.66(t, J=4Hz, 2H, $S\underline{CH_2}CH_2$), 3.7(s, 2H, pyr^a —CH2-S), 6.0-6.6(m, 2H, two NH protons, exchange with deuterium oxide), 7.26(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^a H-3, H-5), 8.53(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^a H-2, H-6).
173a	2-pyridinyl	NCN	cyclopentyl	2120	3480	1.4-2.3(m, 8H, cyclopentyl H-2 to H-5), 2.7(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.7(t, J=7Hz, 2H, $S\underline{CH_2}CH_2$), 3.9(s, 2H, pyr^a $-\underline{CH_2}-S$), 4.25(m, 1H,

Table 24. (cont.)

						cyclopentyl H-1), 6.2-7.03(m, 2H, two NH protons, exchange with deuterium oxide), 7.0-7.46(m, 2H, pyr[a] H-3, H-5), 7.66(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr[a] H-4), 8.46(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr[a] H-6).
173b	3-pyridinyl	NCN	cyclopentyl	2120	3480	1.4-2.26(m, 8H, cyclopentyl H-2 to H-5), 2.73(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.73(t, J=7Hz, 2H, S$\underline{CH_2}$$CH_2$), 3.76(s, 2H, pyr[a] -$\underline{CH_2}$-S), 4.2(m, 1H, cyclopentyl H-1), 6.2-6.73(m, 2H, two NH protons, exchange with deuterium oxide), 7.13-7.46(m, 1H, pyr[a] H-5), 7.6-7.9(m, 1H, pyr[a] H-4), 8.43-8.7(m, 2H, pyr[a] H-2, H-6).
173c	4-pyridinyl	NCN	cyclopentyl	2120	3480	1.13-2.2(m, 8H, cyclopentyl H-2 to H-5), 2.63(t, J=7Hz, 2H, -$\underline{CH_2}$N), 3.33-4.33(m,

Table 24. (cont.)

						5H, pyr^a $-\underline{CH_2}-S$, $S\underline{CH_2}CH_2$ and cyclopentyl H-1), 5.9-6.56(m, 2H, two NH protons, exchange with deuterium oxide), 7.23(d, $J_{2,3}=J_{5,6}=6$Hz, 2H, pyr^a H-3, H-5), 8.5(d, $J_{2,3}=J_{5,6}=6$Hz, 2H, pyr^a H-2, H-6).
174a	2-pyridinyl	NCN	n-butyl	2120	3480	0.94(t, J=7Hz, 3H, CH_3), 1.14-1.8(m, 4H, $NH\text{-}CH_2\underline{CH_2CH_2}$), 2.76(t, J=7Hz, 2H, $-CH_2N$), 3.3-3.6(m, 2H, $NH\underline{CH_2}CH_2$), 3.8(t, J=7Hz, 2H, $S\underline{CH_2}CH_2$), 3.9(s, 2H, pyr^a $-\underline{CH_2}-S$), 6.5(br s, 1H, $\underline{NH}$-n-Bu, exchanges with deuterium oxide), 7.02(br s, 1H, $SCH_2CH_2\underline{NH}$, exchanges with deuterium oxide), 7.16-7.5(m, 2H, pyr^a H-3, H-5), 7.74(d, $J_{3,4}=8$Hz of d, $J_{4,5}=8$Hz of d, $J_{4,6}=2$Hz, 1H, pyr^a H-4), 8.54(d, $J_{5,6}=5$Hz of d, $J_{4,6}=2$Hz, 1H, pyr^a H-6).

Table 24. (cont.)

174b	3-pyridinyl	NCN	n-butyl	2120	3480	1.06(t, J=7Hz, 3H, $-CH_3$), 1.2-1.8(m, 4H, $NHCH_2\underline{CH_2}\underline{CH_2}$), 2.8(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.2-3.63(m, 2H, $NH\underline{CH_2}CH_2$), 3.63-4.1(m, 4H, pyr^a $-\underline{CH_2}-S$, $S-\underline{CH_2}CH_2$), 6.1-6.86(m, 2H, two NH protons, exchange with deuterium oxide), 7.2-7.56(m, 1H, pyr^a H-5), 7.66-8(m, 1H, pyr^a H-4) 8.5-8.83(m, 2H, pyr^a H-2, H-6).
174c	4-pyridinyl	NCN	n-butyl	2120	3480	0.9(t, J=7Hz, 3H, $-CH_3$), 1.06-1.8(m, 4H, $NH-CH_2\underline{CH_2}\underline{CH_2}$), 2.66(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.1-3.53(m, 2H, $NH\underline{CH_2}CH_2-$), 3.7(s, 2H, pyr^a $-\underline{CH_2}-S$), 3.76(t, J=7Hz, 2H, $S\underline{CH_2}CH_2$), 6.33-7.0(m, 2H, two NH protons, exchange with deuterium oxide), 7.26(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^a H-3, H-5), 8.5(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^a H-2, H-6).

Table 24. (cont.)

175a	2-pyridinyl	NCN	n-butyl	2130	3480	0.9(t, J=7Hz, 3H, $CH_2\underline{CH_3}$), 1.23-1.8(m, 2H, $CH_2\underline{CH_2}CH_3$), 2.76(t, J=7Hz, 2H, $\underline{CH_2}N$), 3.43 (m, 2H, $NH\underline{CH_2}CH_2CH_3$, collapses to a triplet after deuterium oxide exchange), 3.76(t, J=7Hz, 2H, $S\underline{CH_2}CH_2$), 3.9(s, 2H, pyr^a -$\underline{CH_2}$-S), 6.36 and 6.93(br s, 1H each, $\underline{NH}$-propyl and S-$CH_2CH_2\underline{NH}$-, exchange with deuterium oxide), 7.2-7.53(m, 2H, pyr^a H-3, H-5), 7.76(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-4), 8.56(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr^a H-6).
175b	3-pyridinyl	NCN	n-propyl	2120	3480	0.9(t, J=7Hz, 3H, -$CH_2\underline{CH_3}$), 1.23-1.83(m, 2H, $CH_2\underline{CH_2}CH_3$), 2.66(t, J=7Hz, 2H, -CH_2N), 3.3(m, 2H, $NH\underline{CH_2}CH_2CH_3$, collapses to a triplet after deuterium oxide exchange), 3.7(t, J=7Hz, 2H,

Table 24. (cont.)

						$S\underline{CH_2}CH_2$), 3.73(s, 2H, pyr^{a} $-\underline{CH_2}-S$), 6.33-6.8(m, 2H, two NH protons, exchange with deuterium oxide), 7.26(d, $J_{4,5}=8Hz$ of d, $J_{5,6}=2Hz$, 1H, pyr^{a} H-5), 7.71(d, $J_{4,5}=8Hz$ of d, $J_{4,6}=4Hz$, 1H, pyr^{a}, H-4), 8.4-8.73(m, 2H, pyr^{a} H-2, H-6).
175c	4-pyridinyl	NCN	n-propyl	2120	3480	0.93(t, J=7Hz, 3H, $-CH_3$), 1.2-1.86(m, 2H, $CH_2\underline{CH_2}CH_3$), 2.7(t, J=7Hz, 2H, $-CH_2N$), 3.3(m, 2H, $NH\underline{CH_2}CH_2CH_3$, collapses to a triplet after deuterium oxide exchange), 3.7(t, J=7Hz, 2H, $S\underline{CH_2}CH_2$), 3.73(s, 2H, pyr^{a} $-\underline{CH_2}-S$), 6.0-6.5(m, 2H, two NH protons, exchange with deuterium oxide), 7.33(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^{a} H-3, H-5), 8.56(d, $J_{2,3}=J_{5,6}=6Hz$, 2H, pyr^{a} H-2, H-6).

Table 24. (cont.)

176a	2-pyridinyl	NCN	ethyl	2120	3480	1.3(t, J=7Hz, 3H, $CH_2\underline{CH_3}$), 2.03(br s, 1H, $\underline{NH}$-Et, exchanges with deuterium oxide), 2.83(t, J=7Hz, 2H, $-\underline{CH_2}N$), 3.4-3.76(m, 2H, $NH\underline{CH_2}CH_3$, collapses to a quartet after deuterium oxide exchange), 3.76(t, J=7Hz, 2H, $S\underline{CH_2}CH_2$), 3.96(s, 2H, pyr[a] $-\underline{CH_2}S$), 6.46(br s, 1H, $CH_2\underline{NH}CSNH$, exchanges with deuterium oxide), 7.16-7.5(m, 2H, pyr[a] H-3, H-5), 7.76(d, $J_{3,4}$=8Hz of d, $J_{4,5}$=8Hz of d, $J_{4,6}$=2Hz, 1H, pyr[a] H-4), 8.63(d, $J_{5,6}$=5Hz of d, $J_{4,6}$=2Hz, 1H, pyr[a] H-6).
176b	3-pyridinyl	NCN	ethyl	2120	3480	1.2(t, J=7Hz, 3H, $CH_2\underline{CH_3}$), 2.7(t, J=7Hz, 2H, $-CH_2N$), 3.2-3.66(m, 2H, $NH\underline{CH_2}CH_3$, collapses to a quartet after deuterium oxide exchange), 3.76(t, J=7Hz, 2H, $S\underline{CH_2}CH_2$), 3.8(s, 2H, pyr[a]

Table 24. (cont.)

						-$\underline{CH}_2$-S), 6.13-6.73(m, 2H, two NH protons, exchange with deuterium oxide), 7.16-7.5(m, 1H, pyr^a H-5), 7.56-7.93(m, 1H, pyr^a H-4), 8.4-8.76(m, 2H, pyr^a H-2, H-6).
176c	4-pyridinyl	NCN	ethyl	2120	3480	1.2(t, J=7Hz, 3H, CH_3), 2.66(t, J=7Hz, 2H, -CH_2N), 3.1-3.56(m, 2H, $NH\underline{CH}_2CH_3$, collapses to a quartet after deuterium oxide exchange), 3.66(t, J=7Hz, 2H, $S\underline{CH}_2CH_2$), 3.7(s, 2H, pyr^a -$\underline{CH}_2$-S), 6.0-6.6(m, 2H, two NH protons, exchange with deuterium oxide), 7.26(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyr^a H-3, H-5), 8.53(d, $J_{2,3}=J_{5,6}$=6Hz, 2H, pyr^a H-2, H-6).

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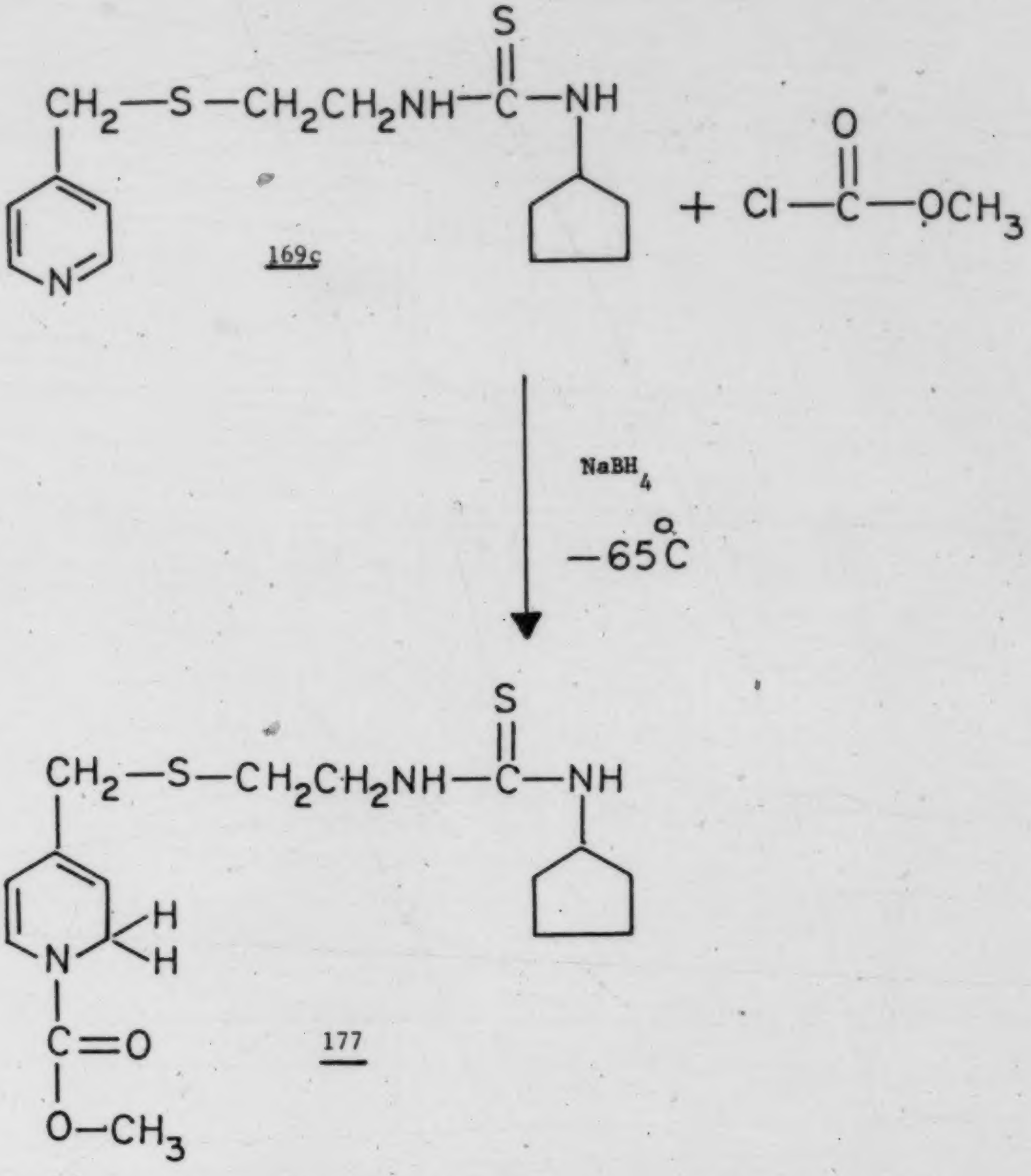
[a] pyr denotes pyridine

summarized in Table 23. Thus, reaction of 102 with cyclopentylisothiocyanate, n-butylisothiocyanate, n-propylisothiocyanate and ethylisothiocyanate gave the respective thioureas 169, 170, 171 and 172. The cyanoguanidines 173, 174, 175 and 176 were prepared by the reaction of 169, 170, 171 and 172 respectively with lead cyanamide in acetonitrile and dimethylformamide. The ir and ^{1}Hnmr data for the thiourea compounds 169-172 and the cyanoguanidines 172-176 are summarized in Table 24. Compounds 169a, 171a, 173a 173c, 175a, 175c have been submitted for testing.

4.3.0.0.0 Synthesis of N-Cyclopentyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl}thiourea 177.

The sodium borohydride reduction of the pyridinyl derivative 169c in the presence of methyl chloroformate in methanol at -65°C yielded the respective 1,2-dihydropyridinyl analog 177 as illustrated in Scheme 13.

The structure assigned to 177 was consistent with its ir, ^{1}H nmr and high resolution mass spectrometric data.

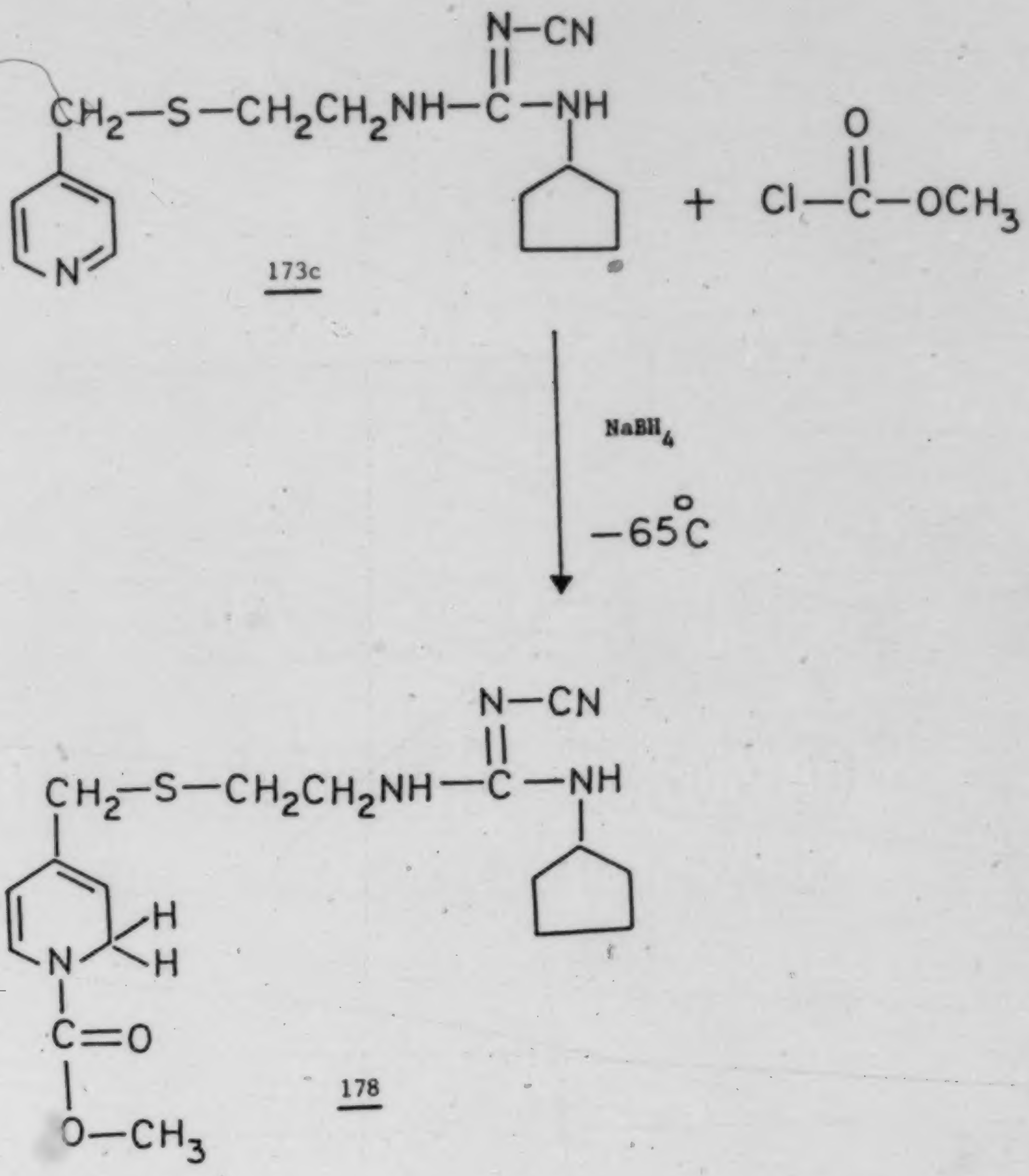

169c
NaBH4
−65°C
177

Scheme 13. Synthetic Route Used for the Synthesis of N-Cyclopentyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl}thiourea 177.

4.4.0.0.0 Synthesis of N"-Cyano-N-cyclopentyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl}guanidine 178.

The sodium borohydride reduction of the pyridine derivative 173c in the presence of methyl chloroformate in methanol at -65°C yielded the respective 1,2-dihydropyridinyl analog 178 as illustrated in Scheme 14.

The structure assigned to 178 was consistent with its ir, ^{1}H nmr and high resolution mass spectrometric data.


173c
NaBH$_4$
−65°C
178

Scheme 14. Synthetic Route Used for the Synthesis of N"-Cyano-N-cyclopentyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl}guanidine 178.

4.5.0.0.0 Pharmacological Evaluation of Histamine H_2-Receptor Antagonistic Activity.

The histamine H_2-receptor antagonist activity of a compound is most conveniently determined in vitro using the chronotropic response of the guinea-pig right atrium or the relaxation of the rat uterus induced by histamine. The nature of the antagonism[170] is determined and quantified from the dose-dependent displacement of the histamine concentration effect curve. The specificity of the H_2-antagonist action can be investigated using preparations such as guinea-pig ileum, which contain only H_1-receptors, and other preparations responsive to agonists such as isoprenaline, a typical β-adrenoceptor stimulant and bethanecol, a cholinergic agent. Inhibition of acid secretion is most easily determined using a perfused stomach preparation in the anaethetised[171] rat where the effect of intravenously administered drug on histamine or pentagastrin-induced gastric acid secretion is determined. Oral activity and the duration of action can be measured using conscious dogs with Heidenhain pouches where it is possible to study the effect of drugs on acid secretion induced by histamine, bethanecol or pentagastrin.[172] Conscious dogs with gastric fistulas are used to study secretory responses to test meals.[173] The H_2-antagonist activity of selected compounds from this study was determined using the guinea pig atria chronotropic response assay by Dr. J.H. McNeill, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver.[139-141]

4.6.0.0.0 Structure-Activity Relationships for Pyridine and Reduced Pyridine Analogs as Histamine H_2-Receptor Antagonists.

Some general structure-activity correlations, based on the test results obtained, describing H_2-receptor antagonist activity for compounds 9 are summarized below.

$$\text{Het-}CH_2SCH_2CH_2\text{NH-Y}$$

1) The H_2-antagonist test results obtained for selected compounds 9 where the Het group was a pyridinyl ring system and Y was C(=x)NHMe where X was S and NCN indicated that the relative activities within these isomeric series were 2-pyridinyl > 4-pyridinyl > 3-pyridinyl. The thiourea analogs were more potent than the corresponding cyanoguanidine analogs.
2) A comparison of the activities of urea (X=O), thiourea (X=S) and cyanoguanidine (X=NCN) analogs of 9 (Y=C(=X)NHMe) where the Het moiety was a 4-(1-methoxycarbonyl-1,2-dihydropyridinyl) substituent indicated that the cyanoguanidine analog was more potent than the urea and thiourea analogs. In the cyanoguanidine series the 4-(1-methoxycarbonyl-1,2-dihydropyridinyl) compound was more active than the 3-(1-methoxycarbonyl) analog. A comparison of the activities for the 4-(1-alkoxycarbonyl-1,2-dihydropyridinyl) compounds in the cyanoguanidine series indicated that the 1-methoxycarbonyl derivative was marginally active whereas the 1-t-butoxycarbonyl and 1-phenoxycarbonyl derivatives were virtually inactive.
3) Compounds 9 having a Het 1-methyl-1,2,3,6-tetrahydropyridinyl

moiety in the cyanoguanidine series (Y=C(=NCN)NHMe) were inactive.

4) Structure-activity correlations 1-3 suggest that the charge distribution in the aromatic pyridine and 1,2-dihydropryidine ring system is important to interaction with the H_2-receptor. The electron density at C-2 < C-4 < C-3 for pyridine while the electron density at C-6 < C-4 < C-5 (C-3) for the N-alkoxycarbonyl -1,2-dihydropyridinyl ring system. On the other hand, the 1-methyl-1,2,3,6-tetrahydropyridinyl ring system does not have an electron deficient carbon adjacent to nitrogen. It is possible that an electron deficient position on the pyridinyl or 1,2-dihydropyridinyl ring of 9 may interact with an electron rich (anionic)site on the H_2-receptor. These results suggest that affinity for the H_2-receptor is due to co-operative and dependent interactions of the molecular substructures (Het and urea, thiourea, or cyanoguanidine moieties) with the receptor.

5) The H_2-antagonist test results obtained for selected compounds 9 where the Het group was a pyridinyl ring system and Y was $C(=CHNO_2)NZ$ where Z was 1-homopiperidinyl, 1-(1,2,3,6-tetrahydropyridinyl) and 1-pyrrolidinyl was consistent with earlier results which showed that the relative activities within an isomeric series was 2-pyridinyl > 4-pyridinyl > 3-pyridinyl. The effect of ring size for the 1-cycloalkylamino substituent Y upon H_2-antagonistic activity was 1-homopiperidinyl > 1-(1,2,3,6-tetrahydropyridinyl) > 1-pyrrolidinyl.

6) Elaboration of compound 9, where the Het group was a pyridinyl ring system and Y was $C(=CHNO_2)Z$ when Z was 1-homopiperidinyl, to

the corresponding 1-methoxycarbonyl-1,2-dihydropyridinyl derivative reduced the H_2-receptor antagonistic activity.

7) Structure-activity correlations 1-6 suggest that the thiourea, cyanoguanidine and nitroethene moieties are bioisosteric groups with respect to their interaction with the H_2-receptor. The pyridine and 1,2-dihydropyridinyl moieties can be considered to be partial bioisosteres.

8) The H_2-antagonist test results obtained for selected compounds 9, where the Het group was a pyridinyl ring system and Y was C(=X)NH-C_6H_5 where X was O, S and NCN indicated these analogs were devoid of H_2-receptor antagonistic acitivity.

9) Elaboration of compound 9 where the Het group was a pyridinyl ring system and Y was C(=S)NH-C_6H_5 to the corresponding 1-methoxycarbonyl-1,2-dihydropyridinyl derivative provided inactive compounds.

10) Compounds 9 having a Het pyridinyl moiety and a C(=$NCOOCH_3$)NH-$COOCH_3$ Y moiety did not possess H_2-receptor antagonistic activity.

11) Elaboration of 9 where the Het group was a pyridinyl ring system and Y was C(=$NCOOCH_3$)$NHCOOCH_3$ to the corresponding 1-methoxycarbonyl-1,2-dihydropyridinyl derivative did not alter activity.

12) The difference in Histamine H_2-receptor antagonistic activity of compounds having a pyridinyl moiety and a 1,2-dihydropyridinyl moiety may be due, at least in part, to the fact that the pyridine moiety is planar while the 1,2-dihydropyridine is non-planar since it is puckered at the C-2 Sp^3 carbon. However the dienamine portion of the 1,2-dihydropyridine ring is relatively flat. A planar heterocyclic ring may be more favourable for interaction with the H_2-receptor since the pyridine analogs were more active than 1,2-dihydropyridine analogs.

5.0.0.0.0 EXPERIMENTAL

Melting pints were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in deuterochloroform unless otherwise stated with TMS as internal standard with a Varian EM-360A or Bruker AM-300 spectrometer. Mass spectra were measured with an AEI-MS-50 mass spectrometer. Exact mass measurements were in many cases used in lieu of microanalytical data. Infrared spectra (potassium bromide unless otherwise noted) were taken on a Perkin Elmer 267 or Nicolet 5DX spectrometer. All of the products described gave rise to a single spot on tlc using three different solvent systems of low, medium and high polarity. Microanalyses were generally within 0.4% of theoretical values. If this was not the case then exact mass measurements were obtained. Preparative thin layer chromatography was performed with 20x20 cm plates using Kieselgel silica gel DF-5 (Camag) 1mm in thickness. All anhydrous reactions were conducted in pre-dried glassware under a positive nitrogen atmosphere. Dry nitrogen gas was obtained by passage through concentrated sulfuric acid, solid potassium hydroxide and then anhydrous calcium sulfate.

5.1.0.0.0 Solvents and Reagents

Dry ether and tetrahydrofuran were distilled from sodium and benzophenone under a nitrogen atmosphere immediately prior to use. Acetonitrile was purified by stirring in the presence of calcium hydride for two hours prior to distillation and storage under an atmosphere of nitrogen.

5.2.0.0.0 Preparation of 2-(3-,4-)Pyridinylcarbinols 99.[174]

The pyridinylcarboxaldehyde 98 (10 g, 93 mmol) was added slowly to a solution of potassium hydroxide (5.23 g, 93 mmol) in 70 mL water with stirring at 0°C since the reaction was exothermic. The mixture solidified to a thick paste which was allowed to stand at 25°C overnight. The reaction mixture was mixed with 150 mL distilled water and the solution was saturated with carbon dioxide gas. The pyridinylcarbinol 99 was extracted with diethyl ether (200 mL) and the ether extract was dried with anhydrous calcium carbonate and filtered. Removal of the solvent *in vacuo* gave a viscus oil which was distilled at 17 torr to yield the pyridinylcarbinol 99.

99a, bp 112-113°C, 59.4% yield.
99b, bp 154-156°C, 55.6% yield.
99c, bp 55-56°C, 58% yield.

5.2.1.0.0 Preparation of 2-(3-,4-)Pyridinylcarbinol hydrochlorides 100.

Anhydrous HCl gas was bubbled slowly into a solution of the pyridinylcarbinol 99 (12 g, 110 mmol) in dry ether (100 mL) until no further precipitation of 100 was observed. Removal of the solvent *in vacuo* and recrystallization of the product from absolute ethyl alcohol gave 100.

100a, mp 100°C, 95% yield.

100b, mp 87°C, 92% yield.

100c, mp 180°C, 85% yield.

5.3.0.0.0 Preparation of 2-(3-,4-)[(2-Aminoethyl)thiomethyl] pyridine dihydrobromides 101.

A solution of the pyridinylcarbinol hydrochloride 100 (10 g, 68 mmol) and cysteamine hydrochloride (8.47 g, 74 mmol, in 48% aqueous HBr (150 mL) was heated under reflux for 18 h. After cooling, the solution was evaporated to dryness and recrystallised from an ethanol-ether mixture to yield 101

101a, mp 175°C, 82.5%

101b, mp 182°C, 80%

101c, mp 238°C, 72.5%

5.4.0.0.0 Preparation of N-Methyl-N'-[2-pyridinylmethylthio) ethyl]ureas 103.

A solution of the amine dihydrobromide 101 (10.0 g, 30.2 mmol) in 25 mL water was basified to pH 8-9 with a solution of potassium carbonate (8.7 g) in water. Removal of the water *in vacuo* and extraction of the residue with isopropanol (4x80 mL) afforded the base 102. The presence of inorganic material in 102 was removed by several evaporation and extraction sequences using isopropanol. Methyl isocyanate (2.3 g, 40 mmol) was added to a solution of the amine 102 obtained above in isopropanol (70 mL) and the mixture was heated at reflux for 2h. Removal of the solvent *in vacuo*, dissolution of the residue in acetone, filtration and removal of the solvent *in vacuo* afforded 103 which was purified on silica gel G plates with chloroform : methanol (8:1 v/v) as the development solvent. Extraction of the band having Rf 0.5 with chloroform : methanol (1:1 v/v) gave 103

5.5.0.0.0 Preparation of N-Methyl-N'-[2-pyridinylmethylthio) ethyl]thioureas 104.

Methyl isothiocyanate (2.3 g, 30 mmol) was added to solution of 102 (5.09 g, 30 mmol) in 70 mL isopropanol and the mixture was heated at reflux for 1.5 h. The solvent was removed *in vacuo*, the residue dissolved in acetone, filtered and the solvent removed *in vacuo* to yield 104. The product was purified on silica gel G plates using chloroform : methanol (8:1 v/v) as development solvent. Extraction of the band having Rf 0.72 with warm absolute ethanol yielded 104 (4.47 g, 65%) as an oil. The product 104 could also be purified by elution from a 2.5 x 20 cm silica gel column with chloroform : methanol (8:1 v/v) as the eluant. Removal of the solvent from the 100-450 mL eluate afforded 104.

5.6.0.0.0 Preparation of N"-Cyano-N-methyl-N'-[2-(pyridinylmethylthio)ethyl]guanidines 105.

Procedure A.

S-Methyl-N-cyano-N'-methylcarbamimidothioate (4.9 g, 30 mmol) was added to a solution of 102 (6.07 g, 36 mmol) in 180 mL acetonitrile and the mixture was heated under reflux with stirring for 48 h. Removal of the solvent *in vacuo* gave a residue which was purified by elution from a 5.5 x 67 cm silica gel column using acetonitrile as eluant. The first 75 mL fraction was discarded. Further elution with acetonitrile (1000 mL) afforded 105.

Procedure B.

Lead cyanamide (2.8 g, 52 mmol) was added to a solution of 104 (6 g, 24 mmol) in 260 mL acetonitrile and 26 mL dimethylformamide. The mixture was heated under reflux with stirring for 48 h during which time additional lead cyanamide (7.8 g) was added in aliquots. The solids were filtered and the solvent was removed *in vacuo* to give the product which was purified by elution from a 7.5 x 50 cm silica gel column using ethyl acetate-isopropanol (1:1 v/v) as eluate. The initial 50 mL fraction was discarded. Further elution (500 mL) gave 105.

5.7.0.0.0 General Synthesis of N-Methyl-N'-{2-[3-(4-)1-alkoxycarbonyl-1,2-dihydropyridinylmethylthio]ethyl}ureas, thioureas and cyanoguanidines 108-125.

Sodium borohydride (0.253 g, 6 mmol) was added to a solution of the desired pyridinyl analog 103-105 b-c (2 mmol) in absolute methanol (10 mL) precooled in a dry ice-isopropanol bath. A solution of methyl chloroformate (phenyl chloroformate or di-tert-butylcarbonate) (2 mmol) in 3 mL dry diethyl ether was added at a rate such that the temperature of the reaction mixture did not rise above -69°C. The reaction was allowed to proceed with stirring at < -69°C for the time specified in Table 7 after which the reaction mixture was allowed to return to 25°C. The reaction mixture was then poured onto ice-water and enough water was added to dissolve the inorganic salts. Extraction with chloroform (4 x 100 mL), washing the combined chloroform extracts with water, drying ($MgSO_4$) and removal of the chloroform *in vacuo* gave the respective 1,2-dihydropyridinyl derivatives 107. The products were purified on silica gel plates using chloroform : methanol (16:1 v/v) as development solvent. The band containing the product (see Rf values listed in Table 7) was extracted with chloroform : methanol (16:1 v/v). When further purification was required, this was effected by elution from a 2.5x20 cm neutral aluminum oxide column using 300 mL chloroform : methanol (1:1 v/v) as eluant.

5.8.0.0.0 Preparation of N"-Cyano-N-methyl-N'-{2-[2-(3-,4-)(1-methylpyridinium)methylthio]ethyl}guanidine iodides 126.

A solution of methyl iodide (6.85 g, 6 mmol) in 10 mL acetone was added to a solution of 105 (0.199 g, 0.8 mmol) in 10 mL acetone. The reaction mixture was heated at reflux for 3 days, cooled and the crystalline product was filtered. Recrystallization from absolute ethanol yielded 126.

5.9.0.0.0 Preparation of N"-Cyano-N-methyl-N'-{2-[2-(5-,4-)(1-methyl-1,2,3,6-tetrahydropyridinyl)methylthio]ethyl}guanidines 127.

A solution of the N-methylpyridinium iodide 126 (0.391 g, 1 mmol) in 20 mL absolute ethanol was cooled to 0°C. Sodium borohydride (0.304 g, 8 mmol) was added slowly and the reduction was allowed to proceed for 5 h at 0°C with stirring. Ice-water (50 mL) was added and the reaction mixture was warmed to 25°C. Extraction with chloroform (4x75 mL) drying (Na_2SO_4) and removal of the solvent *in vacuo* afforded 127. The product was purified by elution from a 2.5 x 20 cm neutral alumina oxide column using 300 mL chloroform : methanol (8:1 v/v) as eluant. Removal of the solvent *in vacuo* gave 127.

6.0.0.0 Preparation of Bis-1,1-thiomethylnitroethene 135.

A) A solution of nitromethane (40 g, 0.655 mol) in carbon disulfide (75.9 g, 60 mL) and absolute ethanol (100 mL) was mixed slowly with a concentrated solution of potassium hydroxide (80 g, 1.43 mol) in ethanol (100 mL) such that a reaction temperature of ~35°C was maintained. A red colour developed and a fine sand colored precipitate separated. Temperatures higher or lower than 35°C resulted in a reduced yield of product 134. The reaction mixture was allowed to stand for 30 min after the addition of ethanolic potassium hydroxide was completed. The mixture was filtered and the solids were washed several times with diethyl ether prior to drying to yield 134 (76.86 g, 55%). Recrystallization of the dipotassium salt 134 from ethanol-water by careful warming gave 134, mp 203°C. Rapid heating may result in an explosion.

B) A solution of the dipotassium salt 134 (10.7 g, 50.2 mmol) in methanol (50 mL) and distilled water (75 mL) was cooled to 0°C and then dimethyl sulfate (12.63 g, 9.5 mL, 75.34 mmol) was added dropwise with stirring at -15°C. When the addition was completed, the reaction mixture was allowed to stand for 1.5 h at 25°C after which it was poured into water (300 mL) with stirring. The product was filtered and recrystallized from methanol in the presence of activated charcoal to give 135 as long yellow needles (6.54 g, 79%), mp 125°C.[175]

6.1.0.0.0 Preparation of N-[2-(Pyridinylmethylthio)ethyl]-1-methylthio-2-nitro-1-ethenediamines 139-141.

A solution of the amine dihydrobromide 101 (10 g, 30.2 mmol) in 25 mL water was basified to pH 8-9 with a solution of potassium carbonate (8.7 g) in water. Removal of the water *in vacuo* and extraction of the residue with isopropanol (4x80 mL) afforded the base 102 The presence of inorganic material in 102 was removed by several evaporation and extraction sequences using isopropanol. *Bis*-1,1-thiomethyl-2-nitroethene 135 (3.35 g, 20 mmol) was added to a solution of 102 in acetonitrile (150 mL) and the mixture was heated at reflux for 48 h. Removal of the solvent *in vacuo* gave a residue which was purified by elution from a 5.5 x 67 cm silica gel column using acetonitrile as eluant. The first 75 mL fraction was discarded. Further elution with acetonitrile (1000 mL) afforded 136.

6.2.0.0.0 General Synthesis of N-[2-(Pyridinylmethylthio)ethyl]-N'-(cycloalkylamino)-2-nitro-1,1-ethenediamines 142-156.

A solution of the secondary amine 137 (7 mmol) in 15 mL absolute ethanol was added to a solution of 136 (1 mmol) in 40 mL absolute ethanol (See Scheme 6). The reaction mixture was heated at reflux for the time specified in Table 14. Removal of the solvent *in vacuo* gave the title compounds 138. The products were purified on silica gel G plates using chloroform : methanol (8:1 v/v) as development solvent. Extraction of the product band (See Rf values in Table 14) with chloroform : methanol (1:1 v/v) was effected. When further purification was required the product was purified by elution from a 2.5 x 60 cm silica gel column using 400 mL chloroform : methanol (1:1 v/v) as eluant to give 138.

6.3.0.0.0 General Synthesis of N-[2-[4-(1-Methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl]-N'-homopiperdinyl(piperidinyl)-2-nitro-1,1-ethenediamines 157 and 158.

Sodium borohydride (0.09 g, 2 mmol) was added to a solution of the pyridinyl analog 147 or 156 (1 mmol) in absolute methanol (10 mL) precooled in a dry-ice isopropanol bath. A solution of methyl chloroformate (0.094 g, 1 mmol) in dry diethyl ether (3 mL) was added at such a rate that the temperature of the reaction mixture did not rise above -69°C. The reaction was allowed to proceed with stirring at < -69°C for 4 h after which the reaction mixture was allowed to return to 25°C. The reaction mixture was poured onto ice-water and sufficient water was added to dissolve the inorganic salts. Extraction with chloroform (4x100 mL), washing the combined chloroform extracts with water, drying (Na_2SO_4) and removal of the chloroform *in vacuo* gave the respective 1,2-dihydropyridinyl analogs 157 from 147 and 158 from 156 The products were purified on silica gel plates, using chloroform : methanol (16:1 v/v) as development solvent. The product band (157, Rf=0.74 and 158 Rf=0.72) was extracted with chloroform : methanol (16:1 v/v). When further purification was required this was effected by elution from a 2.5 x 20 cm neutral alumina oxide column using 300 mL chloroform : methanol (1:1 v/v) as eluant.

6.4.0.0.0 Preparation of N-Phenyl-N'-[2-(pyridinylmethylthio)ethyl]ureas 159 a-c.

Phenyl isocyanate (2.3 g, 19.3 mmol) was added to a solution of 102 (5.09 g, 30 mmol) in isopropanol (70 mL) and the mixture was heated at reflux for the time specified in Table 19. The solvent was removed *in vacuo*. The residue was dissolved in acetone, filtered and the solvent removed *in vacuo*. The residue was dissolved in acetone, filtered and the solvent removed *in vacuo* to yield 159. The product was purified on silica gel G plates using chloroform : methanol (8:1 v/v) as development solvent. Extraction of the band having the Rf listed in Table 19 with warm absolute ethanol yielded 159.

The products 159 could also be purified by elution from a 2.5 x 20 cm silica gel column with chloroform : methanol (8:1 v/v) as the eluant. Removal of the solvent from the 100-450 mL eluate afforded 159.

6.5.0.0.0 Preparation of N-Phenyl-N'-[2-(pyridinylmethylthio)ethyl]thioureas 160 a-c.

Phenyl isothiocyanate (2.3 g, 17 mmol) was added to a solution of 102 (5.09 g, 30 mmol) in isopropanol (70 mL) and the mixture was heated at reflux for the time specified in Table 19. The solvent was removed *in vacuo*, the residue was dissolved in acetone, filtered and the solvent removed *in vacuo* to yield 160. The product was purified on silica gel G plates using chloroform : methanol (8:1 v/v) as development solvent. Extraction of the band having the Rf value listed in Table 19 with chloroform : methanol (1:1 v/v) yielded 160. The products 160 could also be purified by elution from a 2.5 x 20 cm silica gel column with chloroform : methanol (8:1 v/v) as the eluant. Removal of the solvent from the 100-450 mL eluate afforded 160.

6.6.0.0.0 Preparation of N"-Cyano-N-phenyl-N'-[2-(pyridinylmethylthio)ethyl]guanidines 161 a-c.

Lead cyanamide (2.8 g, 52 mmol) was added to a solution of 159 (6 g, 19.8 mmol) in acetonitrile (260 mL) and dimethylformamide (26 mL). The mixture was heated under reflux with stirring for the time specified in Table 19 during which time an additional 7.8 g lead cyanamide was added in aliquots. The solids were filtered and the solvent was removed *in vacuo* to give the product 161 which was purified by elution from a 7.5 x 50 cm silica gel column using ethylacetate : isopropanol (1:1 v/v) as eluate. The initial 50 mL fraction was discarded. Further elution with the same solvent (500 mL) gave 161. The products 161 could also be purified on silica gel G plates with chloroform : methanol (8:1 v/v) as the development solvent. Extraction of the band having the Rf value listed in Table 19 with chloroform : methanol (1:1 v/v) gave 161.

6.7.0.0.0 Synthesis of N-Phenyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl}thiourea 162.

Sodium borohydride (0.253 g, 6 mmol) was added to a solution of 160c (0.606 g, 2 mmol) in absolute methanol (10 mL) precooled in a dry-ice isopropanol bath. A solution of methyl chloroformate (0.189 g, 2 mmol) in dry diethyl ether (3 mL) was added at such a rate that the temperature of the reaction mixture did not rise above -69°C. The reaction was allowed to proceed with stirring at < -69°C for 4 h, after which the reaction mixture was allowed to return to 25°C. The reaction mixture was then poured onto ice-water and enough water was added to dissolve the inorganic salts. Extraction with chloroform (4x100 mL), washing the combined chloroform extracts with water, drying ($MgSO_4$) and removal of the chloroform in vacuo gave the 1-methoxycarbonyl-1,2-dihydropyridinyl product 162. The product was purified on silica gel plates using chloroform : methanol (16:1 v/v) as development solvent. The band containing the product (Rf of 0.73) was extracted with chloroform : methanol (16:1 v/v) to give 162 (0.508 g, 70%) as an oil. When further purification was required, this was effected by elution from a 2.5 x 20 cm neutral aluminum oxide column using 300 mL chloroform : methanol (1:1 v/v) as eluant.

6.8.0.0.0 Preparation of S-Methylisothiourea sulfate 165.[176]

Finely divided thiourea (5 g, 32 mmol) and water (5 mL) were mixed in a 250 mL round bottom flask. Dimethyl sulfate (4.55 g, 32 mmol) was added and an efficient reflux condenser was attached immediately. The reaction was allowed to proceed spontaneously with occasional cooling when the reaction became too rapid and the flask was filled with vapor. When the initial vigorous reaction had subsided, the reaction mixture was heated at reflux for one hour during which time the product crystallized. The reaction was allowed to cool, the flask was removed, 95% ethanol (50 mL) was added and the solid was removed by filtration. The solid was washed with 95% ethanol (2x20 mL) and air dried to give 165 (6.6 g, 72%), mp 232°C (Lit[177], mp 235°C).

6.9.0.0.0 Synthesis of N,N'-Dimethoxycarbonyl-S-methylisothiourea 166.[178]

Methyl isothiourea sulfate 165 (2 g, 7 mmol) was dissolved in 10 mL water at 0°C and then methyl chloroformate (4 g, 42 mmol) and a solution of potassium hydroxide (0.36 g, 6 mmol) in water (10 mL) was added slowly with stirring. The resulting oil was extracted with ether (100 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Cooling and scratching the residue yielded 166 (1g, 67.5%) as white crystals mp 99-101°C. (Lit.,[183] mp 101°C).

7.0.0.0 Synthesis of N,N"-Dimethoxycarbonyl-N'-[2-(pyridinylmethylthio)ethyl]guanidines 167 a-c.

A solution of the amine dihydrobromide 101 (5 g, 15.1 mmol) in water (25 mL) was basified to pH 8-9 with a solution of potassium carbonate (4.35 g) in water. Removal of the water *in vacuo* and extraction of the residue with isopropanol (4 x 80 mL) afforded the free base 102 The presence of inorganic material in 102 was removed by several evaporation and extraction sequences using isopropanol. N,N'-Dimethoxycarbonyl-S-methylisothiourea 166 (3.1 g, 15 mmol) was added to a solution of the amine 102 obtained above in methanol (50 mL) containing a few crystals of *p*-toluenesulfonic acid as catalyst. The mixture was heated at reflux for the time specified in Table 21. Removal of the solvent *in vacuo* gave 167 as an oil which was purified on silica gel G plates using dichloromethane : methanol (9:1 v/v) as development solvent. The product band (See Rf value listed in Table 21) was extracted with dichloromethane : methanol (1:1 v/v). When further purification was required the product was purified by elution from a 2.5 x 60 cm silica gel column using 300-400 mL dichloromethane :

methanol (1:1 v/v) as eluant.

7.1.0.0.0 Synthesis of N,N"-Dimethoxycarbonyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinylmethylthio]ethyl}guanidine 168.

Sodium borohydride (0.14 g, 0.36 mmol) was added to a solution of the pyridinyl analog 167 (0.293 g, 0.9 mmol) in absolute methanol (15 mL) precooled in a dry ice-isopropanol bath. A solution of methyl chloroformate (0.9 mmol) in dry diethyl ether (3 mL) was added at a rate such that the temperature of the reaction mixture did not rise above -69°C. The reaction was allowed to proceed with stirring at ≮ -65°C for 4 h, after which the reaction mixture was poured onto ice-water and sufficient water was added to dissolve the inorganic salts. Extraction with chloroform (3 x 100 mL), washing the combined chloroform extracts with water, drying ($MgSO_4$) and removal of the chloroform *in vacuo* gave the 1,2-dihydropyridinyl derivative 168 The product 168 was purified on silica gel G plates using dichloromethane : methanol (16:1 v/v) as development solvent. The band containing the product 168 (Rf 0.76) was extracted with dichloromethane : methanol (16:1 v/v) to give 168 (0.235 g, 68%) as an oil. When further purification was required this was effected by elution from a 2.5 x 20 cm neutral aluminium oxide column using 300 mL chloroform : methanol 1:1 v/v as eluant.

7.2.0.0.0 General Synthesis of N-Alkyl(cycloalkyl)-N-[2-(pyridinylmethylthio)ethyl]thioureas 169-172.

Cyclopentyl isothiocyanate (n-butyl isothiocyanate, n-propylisothiocyanate or ethyl isothiocyanate) (30 mmol) was added to a solution of 102 (30 mmol) in 70 mL isopropanol and the mixture was heated at reflux for the time specified in Table 23. The solvent was removed *in vacuo*, the residue dissolved in acetone, filtered and the solvent removed *in vacuo* to yield 169 - 172 respectively. The products were purified on silica gel G plates using chloroform : methanol (8:1 v/v) as development solvent. The product band (See Rf values listed in Table 23) were extracted with warm absolute ethanol to give 169 - 172 as oils. The products 169 - 172 could also be purified by elution from a 2.5 x 20 cm silica gel column with chloroform : methanol (8:1 v/v) as the eluant. Removal of the solvent from the 100-450 mL eluate afforded 169 - 172.

7.3.0.0.0 General Synthesis of N-Alkyl(cycloalkyl)-N'-[2-(pyridinylmethylthio)ethyl]cyanoguanidines 173 - 176.

Lead cyanamide (52 mmol) was added to a solution of 169-172 (24 mmol) in 260 mL acetonitrile and 26 mL dimethylformamide. The mixture was heated under reflux with stirring for the time specified in Table 23 during which time additional lead cyanmaide (7.8 g) was added in aliquots. The solids were filtered and the solvent was removed *in vacuo* to give products 173-176 respectively. The products 173 - 176 were purified by elution from a 7.5 x 50 cm silica gel column using ethyl acetate : i-propanol (1:1 v/v) as eluate. The initial 50 mL fraction was discarded. Further elution (500 mL) gave 173 - 176. The products 173 - 176 could also be purified on silica gel G plates using chloroform: methanol (8:1 v/v) as development solvent. Extraction of the product band (Rf values listed in Table 23) with chloroform : methanol (1:1 v/v yielded 173 - 176.

7.4.0.0.0 Preparation of N-Cyclopentyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl}thiourea 177.

Sodium borohydride (0.228 g, 6 mmol) was added to a solution of 169 (0.295 g, 1 mmol) in absolute methanol (10 mL) precooled in a dry ice-isopropanol bath. A solution of methyl chloroformate (0.189g, 2 mmol) in a dry diethyl ether (3 mL) was added at such a rate that the temperature of the reaction did not rise above -69°C. The reaction was allowed to proceed with stirring at <-69°C for 4 h, after which the reaction mixture was allowed to return to 25°C. The reaction mixture was then poured onto ice-water and enough water was added to dissolve the inorganic salts. Extraction with chloroform (4 x 100 mL), washing the combined chloroform extracts with water, drying ($MgSO_4$) and removal of the chloroform *in vacuo* gave the 1-methoxycarbonyl-1,2-dihydropyridinyl product 177. The product was purified on silica gel plates using chloroform : methanol (16:1 v/v) as development solvent. The band containing the product (Rf of 0.7) was extracted with chloroform : methanol (16:1 v/v) to give 177 (0.213 g, 60%) as an oil. When further purification was required this was effected by elution from a 2.5 x 20 cm neutral aluminium oxide column using 300 mL chloroform : methanol (1:1 v/v) as eluant. The spectral data for 177 is listed below: ir(KBr), NH absorption at 3280, a C=S absorption at 1090 and a C=O absorption at 1710 cm^{-1}. The ^{1}H nmr ($CDCl_3$) δ, 8H multiplet at 1.25-2.22 assigned to the cyclopentyl H-2 to H-5 protons, a 2H triplet (J=7Hz) at 2.6 assigned to the -CH_2-N, a 2H singlet at 3.07 due to the dihydropyridinyl -CH_2-S), a 2H triplet (J=7Hz) at 3.57 assigned to S$CH_2$$CH_2$N, a 3H singlet at 3.75 due to O-CH_3, a 1H multiplet at 3.9-4.2

assigned to the cyclopentyl H_1 proton, a 2H doublet (J_{gem}=3Hz) at 4.27 due to the dihydropyridinyl H-2, a 1H multiplet at 5.2 due to H-5, a 1H multiplet at 5.35 attributed to H-3, a 2H multiplet at 6.32 assigned to the two NH protons and a 1H doublet ($J_{5,6}$=8Hz) at 6.7 assigned to the dihydropyridinyl H-6; Exact Mass calcd. for $C_{16}H_{25}N_3O_2S_2^{32}$: 355.1389; found: 355.1389.

7.5.0.0.0 Preparation of N"-Cyano-N-cyclopentyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridinyl)methylthio]ethyl}guanidine 178.

Sodium borohydride (0.3 g, 7.89 mmol) was added to a solution of 173c (0.303 g, 1 mmol) in absolute methanol (10 mL) precooled in a dry ice-isopropanol bath. A solution of methyl chloroformate (0.189 g, 2 mmol) in dry diethyl ether (3 mL) was added at a rate such that the temperature of the reaction mixture did not rise above -69°C. The reaction was allowed to proceed with stirring at $\leq$ -69°C for 4 h, after which the reaction mixture was allowed to return to 25°C. The reaction mixture was then poured onto ice-water and enough water was added to dissolve the inorganic salts. Extraction with chloroform (4 x 100 mL), washing the combined chloroform extracts with water, drying ($MgSO_4$) and removal of the chloroform *in vacuo* gave the 1-methoxycarbonyl-1,2-dihydropyridinyl product 178. The product was purified on silica gel plates using dichloromethane : methanol (16:1 v/v) as development solvent. The band containing the product (Rf of 0.72) was extracted with chloroform : methanol (16:1 v/v) to give 178 (0.246 g, 68%) as an oil. When further purification was required this was effected by elution from a 2.5 x 20 cm neutral aluminium oxide column using 300 mL chloroform : methanol (1:1 v/v) as eluant. The spectral data for 178 is listed below: ir (KBr), NH absorption at 3480, aCN absorption at 2160 and a CO group absorption at 1710 cm^{-1}. The ^{1}H nmr ($CDCl_3$) , 8H multiplet at 1.25-2.22 assigned to the cyclopentyl H-2 to H-5 protons, a 2H triplet (J=7Hz) at 2.6 assigned to the -$\underline{CH_2}$N, a2H singlet at 3.07 due to the dihydropyridinyl -$\underline{CH_2}$-S, a 2H triplet (J=7Hz) at 3.7 assigned to S$\underline{CH_2}$ CH_2N, a 3H singlet at 3.75 due to the -O$\underline{CH_3}$, a 1H multiplet at 3.9-4.2 assigned to the cyclopentyl H-1 proton, a 2H doublet (J_{gem}=3Hz) at 4.27 due to the dihydropyridinyl H-2, a 1H multiplet at 5.2 due to H-5, a 1H multiplet at 5.35 attributed to H-3, a 2H multiplet at 6.32 assigned to the two NH protons and a 1H doublet ($J_{5,6}$=8Hz) at 6.7 assigned to the dihydropyridinyl H-6; Exact Mass calcd. for $C_{17}H_{25}N_5O_2S^{32}$ 363.1729;found; 363.1733

7.6.0.0.0 Guinea Pig Atria Chronotropic Response.

Hartley guinea pigs of either sex, 350-450 g, were stunned by a blow to the head. Following cervical dislocation, the heart was removed and the right atria detached and suspended in Chenoweth-Koelle buffer (pH 7.4) containing a 10^{-6} M concentration of timolol at 37°C in isolated tissue baths. The atria were dissected and suspended at 1g resting tension in tissue baths maintained at 37°C. Contractions were measured isometrically with a Grass force-displacement transducer. Spontaneous contractions commenced within five min and the frequency of these contractions was used as the index of stimulation in response to increasing doses of histamine dihydrochloride. Following a 45 min equilibration cumulative dose response curves for the agonist histamine dihydrochloride (increments of half-log units from 10^{-8}M to 3×10^{-5}M) were prepared. The response of the tissue to each dose of agonist was allowed to develop and plateau (about 2 min per dose) prior to administration of the next higher dose. Immediately following development of the final response, tissues were washed and allowed to return to basal frequencies (about 45 min). The buffer was changed every 10-15 min during this period. Upon completion of the agonist cumulative dose-response curve, the atria were allowed to equilibrate for a minimum of 30 min. The test compound (antagonist) was then added to six of the eight tissue baths at a concentration of 3×10^{-5}M or 10^{-4}M and incubated for 30 min. The remaining two tissue baths received an equal amount of vehicle used to dissolve the test compound. Following a 30 min incubation, histamine dihydrochloride was added to all eight baths as described for the histamine dose-response curve. The only variation in protocol was the allowance of an additional 1-2 min for development and plateau of the response to higher concentrations of agonist necessitated by the inhibition exhibited by some test compounds (antagonists). Subsequent dose-response curves to histamine dihydrochloride were carried out as described above using increasing concentrations of the test compound, not exceeding three concentrations of test compound per tissue. When the volume of the vehicle containing the test compound was increased, the volume of vehicle added to control tissue baths were increased accordingly. When sufficient data were acquired, usually 4-6 tissues subjected to three concentrations of the test compound, the number of beats per min for each dose of histamine dihydrochloride was counted. ED_{50} values for each dose-response curve were established and pA_2 values were calculated according to the method of Schild.[179] The H_2-antagonist testing was performed by Dr. J.H. McNeill, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, B.C.

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